ANNALS OF
INTERNAL MEDICINE

VOLUME 47 NOVEMBER, 1957 NUMBER 5

OUR GROWING UNDERSTANDING OF THYROID FUNCTION AND ITS CLINICAL APPLICATION *

By J. HOWARD MEANS, M.D., F.A.C.P., *Boston, Massachusetts*

IT is a great pleasure, ladies and gentlemen, for me to address the College once more on a subject long dear to me—the thyroid. The justification for attempting so comprehensive an approach in so short a time is that, because I am older than most of you, I can perhaps give a perspective in depth which those of you who have come into the field more recently cannot have got by personal experience.

As far as I can recall, I first met the thyroid when I was a freshman in Harvard College in 1904. In an elementary course in anatomy, physiology and hygiene, we were told of an organ in the neck—the thyroid gland—atrophy of which gave rise to a clinical picture called myxedema. We were shown pictures of such patients, and they made a lasting impression on me. It had already been known then for about a dozen years that feeding thyroid would completely relieve this disturbance, and from that fact had been derived the concept of an internal secretory function of the thyroid. The only other endocrinologic recollection of that course was some pictures of acromegalics, and we were told this condition was somehow related to the pituitary.

Aside from the effect of castration, knowledge of which goes back to antiquity, the first significant endocrinologic observation was that of Addison (1855) on the effects of destruction of the suprarenal capsules, as they were then called. I mention these things to indicate that most of the great original basic concepts of endocrinology arose in the clinic. The original concept of internal secretion was discovered through observation of

*Presented at the Thirty-eighth Annual Session of The American College of Physicians, Boston, Massachusetts, April 12, 1957.

Requests for reprints should be addressed to J. Howard Means, M.D., 60 Mount Vernon Street, Boston 8, Massachusetts.

Copyright ©, 1957, by The American College of Physicians

the effects of the destruction of various glands by disease, or their removal by surgeons, or through successful substitution therapy, of which the first was with thyroid. This is a powerful argument in favor of clinical investigation—that is to say, research upon patients.

The follow-up by the methods of basic science of the phenomena clamoring for interpretation which nature turns up in the shape of illness is the modus operandi of progress in scientific medicine. Furthermore, contrasting morbid processes with normal ones deepens our understanding of the latter. Clinical research is therefore a powerful cross-fertilizing influence in the so-called pure sciences of biology, biochemistry and biophysics. It broadens their scope and increases the perspicacity of their devotees.

I became concerned with the thyroid in this spirit, but in a very primitive fashion, as early as 1914. In those days our concept of thyroid function was decidedly restricted. We thought of the thyroid as a highly specialized organ, making a hormone (the word had then but very recently been introduced by the great English physiologist Starling) which conveyed special messages to target organs or tissues throughout the body. The hormone itself had not then been identified, although the fact that it uniquely requires iodine for the fulfilment of its function was known to us. That the action of this still elusive hormone on targets is characteristically calorigenic, but also that it has to do with growth and development, was common knowledge. It was because of the calorigenic property that we started our investigations in this field with the aid of metabolimeters. Just what regulated the rate of function of the thyroid system was enshrouded in mystery. Was the supply of thyroid determined by the demand for oxygen by the tissues, or vice versa? The modern concept of servo or feed-back systems had not then entered our thinking.

The concept of a thyrotropic action by the anterior pituitary did not emerge in any effective way until around 1930. However, a hint was given over 100 years ago when, in 1851, the French physician Nièpce [1] found that the pituitary is hypertrophied in endemic cretinism. This hint remained untaken for some seven decades, but then quite suddenly there burst upon us, from several quarters, evidence of a highly significant hook-up, reciprocal in nature, between the anterior pituitary and the thyroid. Thus entered the pituitary-thyroid axis as Salter,[2] I think, first called it—a true feed-back or servo-mechanism, in modern parlance. In the 1940's Rawson,[3] in our clinic, made extensive studies using his cell height and tissue culture technics on both qualitative and quantitative aspects of thyrotropic function.

At the same time other endocrine servo-mechanisms, pituitary-gonad, pituitary-cortex, etc., were coming to the fore, and by degrees a larger concept of the endocrine system as a great, bodywide coördinating mechanism, working through a congeries of glandular servo-mechanisms, began to take form. The beginning of such an idea was probably in the mind of Claude Bernard as early as the 1850's, and certainly Starling in 1906 regarded the

system of glands of internal secretion as a means of coördinating the activities of the various parts of a complex organism. He even drew a parallel with the nervous system, and suggested that the endocrine might be the more ancient. Certainly we can conceive of the nervous system and the endocrine system as the two great integrating mechanisms of the animal body. Furthermore, these two must of necessity be integrated each with the other. How this nervous-endocrine hookup occurs, via neuro-humoral pathways between the hypothalamus and the pituitary, is of recent years being gradually clarified.

At the basic science level progress is made by experiment, and the scope of experiment is determined by the potentialities of tools. Electron microscopes, ultracentrifuges and other such gadgets have greatly increased the power of the investigator to penetrate certain areas. In the field of basic thyroidology, of really revolutionary importance are such methods as the radioactive labeling of iodine (and, very recently, of other elements), chromatography, which permits easy separation of chemical substances in biologic materials, and the availability of agents which permit the experimenter to turn thyroid function on or off at will. In this latter connection I refer, of course, to thyrotropin on the one hand, and the antithyroid drugs on the other. By means of these methods and others, a great ebullition of basic thyroid research has taken place involving many foci of activity, both in the United States and abroad, especially since the end of World War II.

The line taken in all this has been for the most part that of tracing the biosynthesis of thyroid hormone (or now, perhaps, we must say hormones), and its or their transport, actions on targets, and final degradation in the body. By means of the methods of enzyme chemistry it is becoming possible to look within target cells and observe the effects which hormones have upon their internal workings.

The laboratory synthesis of thyroxine by Harington and Barger in 1927 [4] was a great milestone. Since that time every effort has been made to discover how nature synthesizes it. Certain facts have been fairly well established; others, more elusive, are the subjects of hot pursuit.

The steps in the biosynthetic process within the thyroid are now generally accepted to be as follows: In the first place, it is known that the thyroid has the unique power of trapping iodine, which reaches it via the blood stream as iodide. The precise nature of the trapping mechanism has yet to be identified. After trapping, according to Harington's classic work, there is this sequence: oxidation of iodide to iodine, iodination of tyrosine to form diiodotyrosine, then coupling of two molecules of diiodotyrosine, with the loss of one side chain, to form thyroxine. It is further believed that the thyroid parenchymal cells also elaborate a special protein—thyroglobulin—and that it is within the matrix of this protein that the steps in the biosynthesis of thyroxine take place.

According to Salter,[2] thyroglobulin can be secreted even in the absence

of iodine, and it will be laid down in the thyroid follicles as colloid. This is what happens in iodine-want goiter. Such colloid may have but little physiologic activity, but when iodine is exhibited under such circumstances, there may be rapid iodination of the colloid, which thus acquires physiologic activity and release of an excess of hormone from the gland, so that the patient may become temporarily thyrotoxic. Something of this sort is probably what happens in what the Swiss have called Iodbasedow.

There is now, however, more to the story than that. The advent of radioactive labeling and of separation by chromatography discloses that there are other iodinated tyrosines and thyronines in the thyroid than just diiodotyrosine and thyroxine (tetraiodothyronine). The list at present contains also monoiodotyrosine, triiodothyronine and, recently, diiodothyronine. There may be others, but the question arises, What are the rôles of all of them? It could be that they are merely useless by-products which a profligate nature cannot help making as she makes the substance she is really after. The fact that enzymes exist which can bring about their deiodination, thus permitting them to be catabolized and got rid of, lends support to such a theory.

Until all this recent work, it was generally accepted that thyroxine is the one and only true thyroid hormone. All changes made in its molecule had diminished or abolished its hormonic activity. In 1953, however, Gross and Pitt-Rivers found that triiodothyronine, which is naturally present in the thyroid, not only exerts all the physiologic actions of thyroxine, but also does so more expeditiously. Pitt-Rivers therefore properly asked the question, "What are the thyroid hormones?" This cannot yet be finally answered. All that can be said is that both thyroxine and triiodothyronine are present in the thyroid gland and in the blood, and that both show the physiologic properties characteristic of thyroid function, that is to say, relief of athyreosis.

As to the storage of thyroid hormone, it seems clear now that it is in the form of iodinated thyroglobulin within the acini of the thyroid follicles. Presumably incorporated within the long filamentous molecule of this protein are numbers of all of the iodinated amino acids which I have enumerated, probably arranged according to some significant pattern. When there is an environmental shortage of iodine, some or all of these will be in short supply.

Release of hormone from the thyroid is believed to be accomplished by the action of proteolytic enzymes on the colloid, or stored thyroglobulin, which breaks it down into smaller molecules which can diffuse out of the gland into the blood stream, and in the blood stream are known to be carried in loose combination with plasma proteins. How hormones are unloaded from such combination, or how they act upon target cells, or how they are finally disposed of, is still in the realm of conjecture. It is interesting, in this connection, that two new iodine-bearing amino acids, the acetic

acid homologues of triiodothyronine and of thyroxine, known popularly as TRIAC and TETRAC,[6] have been found by several investigators not in the thyroid, but in the kidney. They may represent a peripheral stage in the transformations of thyroid hormone, produced perhaps at the time of impingement of hormone on target.

The intensive research attack, therefore, has now moved into the target, that is to say, to the cellular level. The cell is being dissected and the movement of labeled thyronines through it is being investigated. Homogenation and centrifugation at very high speeds permit the separation of various parts of the cell's structure one from another. Mitochondria, for example, which seem to be the centers of energy transformations within the cell, can be studied apart from those elements which have to do with protein synthesis and mitosis.

While all such basic work is going on, the clinic is always nearby. It is pleasant to recall in this connection that as long ago as 1916 Emil Goetsch [7] was keen enough to observe that the number of mitochondria in the cells of certain hyperactive thyroids was increased over those found in normal thyroid cells, and with great foresight he concluded that mitochondria bear some relationship to the secretory activity of the cell. If he had said metabolic activity and had extended his hypothesis to include all cells, he would have been close to where the cytologists are working today. Goetsch is a surgeon, but he had, in this instance at least, an insight into the significance of a basic biologic fact which was truly prophetic. Actually, I do not know of any field in which research and practice go along hand in hand more helpfully one to the other than they do in endocrinology. Such certainly has been the case in our group of workers on the thyroid, and such very notably was the case in all of Fuller Albright's work in other fields of endocrinology.

And now let us look for some of the more important practical applications of our growing understanding of the basic biology of the thyroid. Actually, the development of substitution therapy with thyroid in states of hypothyroidism, or athyreosis, and the prophylaxis of endemic goiter by means of iodine, may be said to be the first of such applications. We are concerned now, however, with more recent ones.

When it became known in 1936 that iodine can be made temporarily radioactive, the basic knowledge that the thyroid has a specific affinity for that element suggested at once that advantage could be taken of this fact, not only to label iodine for research purposes, but also to use it for diagnostic and therapeutic purposes.[8]

By labeling iodine through the expedient of making it radioactive, one can determine the rate of uptake of iodine by the thyroid, either by observing how much of a given amount of radiation can be detected by means of counters placed over the gland, or by observing the difference between the amount of radiation administered and that which appears in the urine. The

assumption is made that what does not come out in the urine is retained in the thyroid.

The measurement of rate of uptake of I^{131} can usefully be compared with basal metabolic rate and the level of protein-bound iodine in the blood. All such measurements are in a way indices of thyroid function, but comparison of them one with the other permits a broader understanding of a subject's total thyroid function than any one of them alone, for the reason that they test different aspects of thyroid function.

In obscure cases, or in cases where the picture has been mixed up by prior treatment, the use of the whole battery of tests can be very helpful. You have here an analogy with the testing of liver function by means of multiple tests.

Various refinements of the diagnostic use of radioiodine uptake have emerged—regional scanning, for instance, which permits identification of differences in function between one part of the thyroid and others, hot nodules from cold nodules, and that sort of thing.

Then, too, there is the method of autoradiography by which one can observe microscopically which thyroid cells take up iodine and which do not. All such procedures have greatly extended the scope of diagnosis of function in disorders of the thyroid.

Radioiodine is useful in the treatment of certain thyroid diseases, solely because it permits implantation of destructive doses of radiation directly within the parenchymal cells of the thyroid gland. The indications for its use, like those for surgical thyroidectomy, are in cases where it is desired to suppress or destroy thyroid tissue, namely, in hyperthyroidism or in cancer of the thyroid. You can use it also if you want to produce hypothyroidism, as treatment for certain types of heart disease.

In my opinion, radioiodine therapy is the best therapy for the thyrotoxicosis of Graves's disease that has yet been devised. Of course it is not a treatment based on any knowledge of the cause of Graves's disease, which still is unknown. Indeed, the cause of Graves's disease remains a challenge to the investigator. The use of radioiodine in the treatment of cancer of the thyroid is very limited, for many such cancers will not collect iodine, so one can get no radiation into them by this method. Time does not permit me to discuss these matters further. Nor have I time to discuss the question of whether triiodothyronine offers any therapeutic advantage over thyroxine. This matter I consider, anyway, to be still in the realm of the controversial.

I would like now to speak of iodine-want goiter. There are two kinds —extrinsic and intrinsic. Extrinsic iodine-want goiter is the familiar endemic goiter seen in regions in which the environment is poor in iodine. It is a deficiency syndrome. Intrinsic iodine-want goiter presents clinically an identical picture. We used to call it sporadic colloid goiter, and wondered what produced it in regions where the environment had a plentiful supply

of iodine. The newer methods of research which I have mentioned have raised the curtain considerably on this problem. Such goiters are also due to iodine-want, but to one which comes about through an internal defect in utilization of iodine, not to an external shortage in the supply of iodine or to the presence of an environmental goitrogen. Various recent studies in Boston, in Leiden and in Glasgow by Stanbury, Querido, McGirr [9] and others have disclosed that in such cases of sporadic nontoxic goiter defects can be found in the assembly line of hormone biosynthesis. In some cases the defect is at one step, in others at another. The defects are probably due to the lack in each type of a specific enzyme. In one variety that has been identified, there was an inability to perform the iodide-to-iodine step. In another the difficulty was with the coupling of tyrosines to produce thyronines. In a third there was a block into the deiodination of diiodotyrosine. This last caused a great loss of iodine in the urine and a state of iodine starvation in the subject. In all of these types the end result is an inability to complete the biosynthesis of thyroid hormone, with resulting compensatory goiter, and finally clinical hypothyroidism. The pinpointing of the functional defect would have been impossible without the new methods of investigation. These defects often run in families, and undoubtedly have a hereditary component. It is altogether likely that Graves's disease also has a hereditary component, and it can be expected, indeed, that the geneticist will play an increasingly important role in the future in the search for the final causes of these disorders involving the thyroid.

It is necessary now to close this discussion. I have tried to give you an indication of the direction and character of research in thyroidology, and of the interdependence of research and practice, not only in this field but also in all fields of medicine, if any progress is to be made.

Summario in Interlingua

Le passate 20 annos ha vidite un expansion rapide de nostre cognoscentias in re le biosynthese del hormon o del hormones thyroide como etiam in re lor transporto, lor metabolismo, e lor effectos al punctos de destination. Nove methodos technic ha contribuite grandemente a iste progresso.

De importantia eminente inter istos esseva le uso de isotopos radioactive de iodo (per que moleculas iodifere pote esser marcate e traciate) e de chromatographia (per que tal moleculas es facile a separar).

Le investigation del function thyroide ha etiam profitate enormemente del introduction de thyrotropina e le drogas antithyroide que permitte le activation e interruption arbitrari del biosynthese de hormon thyroide.

Tal studios fundamental trova applicationes practic in le diagnose e le therapia. Le prime de istos esseva le utilisation de iodo radioactive in mesurar le acceptation de iodo per le thyroide como adjuta in le diagnose de hyper- e hypothyroidismo. In le therapia, radioiodo ha essite usate pro occider cellulas thyroide in thyrotoxicosis e etiam in cancere.

Plus recentemente le uso diagnostic de radioiodo ha essite applicate a objectivos minus restringite. In certe casos de struma con hypothyroidismo, appropriate methodos de radiomarcation rende possibile precisar le puncto de blocage per que le

processo del biosynthese del hormon es disrumpite. Etiam defectos in le metabolismo hormonic es discoperite, e il es ben possibile que certes de istos va contribuer al clarification del etiologia de morbo de Graves. Ambe iste defectos—i.e. defectos de synthese e defectos de metabolismo—pote esser hereditari. Per consequente nos nunc require le assistentia del geneticos.

BIBLIOGRAPHY

1. Nièpce, B.: Traité du goitre et du crétinisme. Suivi de la statistique des goitreux et des crétin dans le bassin de l'Isère en Savoie, dans les départments de l'Isère, des Hautes-Alpes et des Basses-Alpes, 1851, J. B. Baillière, Paris.
2. Salter, W. T.: The endocrine function of iodine, 1940, Cambridge, Harvard University Press.
3. Rawson, R. W., Graham, R. M., and Riddell, C. B.: Physiological reactions of the thyroid stimulating hormone of the pituitary, Ann. Int. Med. **19**: 405, 1943.
4. Harington, C. R., and Barger, G.: Chemistry of thyroxine. III. Constitution and synthesis of thyroxine, Biochem. J. **21**: 456, 1927.
5. Gross, J., and Pitt-Rivers, R.: 3:5:3' Triiodothyronine; isolation from the thyroid gland and synthesis, Biochem. J. **53**: 652, 1953.
6. Pitt-Rivers, R.: Physiological activity of the acetic acid analogues of some iodinated thyronines, Lancet **2**: 234, 1953.
7. Goetsch, E.: Functional significance of mitochondria in toxic thyroid adenomata, Bull. Johns Hopkins Hosp. **27**: 192, 1916.
8. Means, J. H.: The thyroid and its diseases, 2nd Ed., 1948, J. B. Lippincott Co. Philadelphia.
9. Stanbury, J. B., and McGirr, E. M.: Sporadic or non-endemic familial cretinism with goiter, Am. J. Med. **22**: 712, 1957.

THE SIGNIFICANCE OF BACTERIAL HYPERSENSITIVITY IN HUMAN BRUCELLOSIS: STUDIES ON INFECTION DUE TO STRAIN 19 *BRUCELLA ABORTUS**

By Wesley W. Spink, M.D., F.A.C.P., *Minneapolis, Minnesota*

Although the host-parasite relationship in many infectious diseases has been intensively studied in man, it is surprising how little is known about the fundamental mechanisms that are responsible for the resultant human illness. In conjunction with studies on the host-parasite factors in brucellosis, my associates and I have sought an answer to the question, What basic features contribute to the illness of a patient with this disease?

The purpose of this report is to point out the significance of bacterial hypersensitivity in the genesis of the illness caused by brucella organisms. Such a thesis has been proposed by others, not only for brucellosis but also for many other infectious diseases. But direct support for this concept in man has often lacked precise data. While several investigators have emphasized the marked hypersensitivity to brucella antigens possessed by patients with chronic brucellosis, little information is available relative to the significance of such hypersensitivity during the initial phase of the illness. In prosecuting this problem we were most fortunate in being able to observe the sequence of clinical and immunologic events in four veterinarians, each of whom developed brucellosis following accidental inoculation of themselves with living organisms of strain 19 *Brucella abortus.* Such an opportunity is rarely encountered. There are only four reports in the medical literature on human brucellosis due to strain 19.[1-4] Our own observations were made over a period of seven years. These accidental infections provided an excellent chance to study the natural course of brucellosis. We knew precisely when the patients became infected, and the subsequent course of events was followed closely.

Strain 19 is a stable variant of *Br. abortus,* with attenuated virulence for animals, and probably for man. Because it is a good antigen, and because it has a mild degree of virulence, the living organisms of strain 19 are used extensively and successfully for purposes of immunizing cattle against Bang's disease, or "contagious abortion." From an immunologic point of view, strain 19 is to brucellosis what BCG vaccine is to tuberculosis.

Two points must be emphasized in interpreting the sequence of clinical

* Presented at the Thirty-eighth Annual Session of The American College of Physicians, Boston, Massachusetts, April 11, 1957.

From the Department of Medicine, University of Minnesota Hospitals and Medical School.

Requests for reprints should be addressed to Wesley W. Spink, M.D., Department of Medicine, University of Minnesota Medical School, Minneapolis 14, Minnesota.

and immunologic changes that occurred in the patients. First, although strain 19 has attenuated virulence for both man and animals, the acute illness in the four veterinarians varied from mild to severe states. In addition, the illness was definitely related to acquired and specific bacterial hypersensitivity. Second, the four patients displayed two fundamental differences in their immune status before becoming infected. Two of the men had neither historical nor immunologic evidence of a brucella infection prior to their accident. In contrast, the two other men had had brucellosis previously. We had, then, two individuals without hypersensitivity to brucella organisms before they were accidentally infected, and two who had already acquired brucella hypersensitivity. As a result of the presence or absence of acquired bacterial hypersensitivity, the immediate course of events following infection in the two groups of patients was quite different.

Case Reports

The course of illness in two men who had neither historical nor immunologic evidence of brucellosis prior to being accidentally infected with strain 19 Br. abortus.

Case 1. The course of this patient's illness has been detailed elsewhere.[2] Briefly, he was a 25 year old white student of veterinary medicine at the University of Minnesota. During a vacation period he assisted a veterinarian immunize cattle with strain 19. It was definitely known that just prior to this temporary work brucella agglutinins were absent from his blood, and he had had no historical evidence of having had brucellosis. During an attempt to inject vaccine into a calf the syringe separated from the needle, and a considerable portion of the suspended living organisms contained in the syringe splashed into his eyes. The course of events in this patient following this accident is shown in figure 1. *It is to be noted that he was entirely asymptomatic for seven days following the introduction of brucella organisms into his conjunctivae.* He developed muscle aches on the eighth day, followed by chills and fever. On the eleventh day he entered the hospital quite ill. His temperature approached 106° F., and he had shaking chills. A tender and enlarged spleen was palpated. Twelve days after the accident strain 19 was isolated from his blood stream, and the serum brucella agglutinin titer was 1 to 320. An intradermal test with brucellergen was positive. He was treated with chlortetracycline and dihydrostreptomycin; he recovered and has remained well.

Case 2. The patient was a 23 year old white student of veterinary medicine at the University of Minnesota, who also was engaged in aiding a veterinarian immunize cattle during a vacation period. He had had no previous history of having had brucellosis, and brucella agglutinins were absent from his blood just two days before he went to work. During an attempt to inoculate a calf the syringe became separated from the needle and his left eye was exposed to a suspension of living organisms. The subsequent course of events is presented in figure 2. He remained in good health for 10 days after the accident. On the eleventh day he did not feel well, complaining of a stiff neck and headache. He felt toxic, the headache increased in severity, and he perspired more than usual. He sought medical attention. At first, infectious mononucleosis was suspected. But 12 days after the accident brucella agglutinins were present in his blood in a titer of 1 to 40. Five days later the titer was 1 to 160. Strain 19 was isolated from his blood 14 and 17 days after the accident.

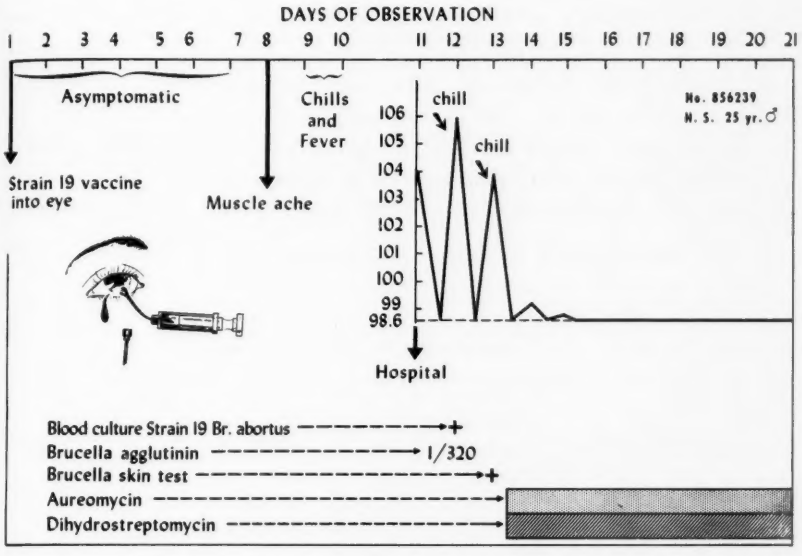


FIG. 1. The clinical course of a veterinarian who accidentally infected himself in the eyes with strain 19 *Br. abortus*. Note the latent period of eight days before the onset of symptoms. He was acutely ill, with a temperature of almost 106° F.

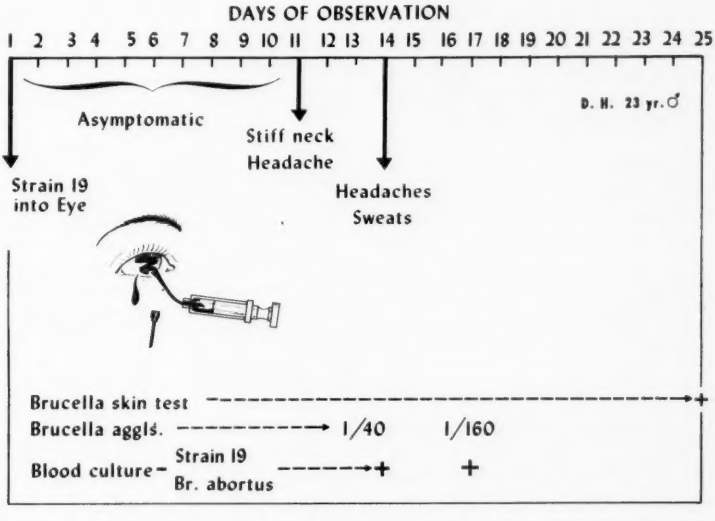


FIG. 2. The clinical course of a veterinarian who infected himself in the eye with strain 19 *Br. abortus*. A latent period of 10 days ensued before the first appearance of symptoms. He had a mild illness, although strain 19 was isolated from his blood on two occasions.

His maximal temperature was 100.3° F. A brucella skin test applied 25 days after the introduction of brucella organisms into his eyes produced chills, fever, sweats and headache. He was treated with tetracycline and recovered. One year later, as a practicing veterinarian, he was well, and brucella agglutinins were absent from his blood.

The important feature in these two patients is that eight and 10 days, respectively, elapsed from the time brucella organisms were introduced into the body until the first symptoms of illness appeared. The significance of

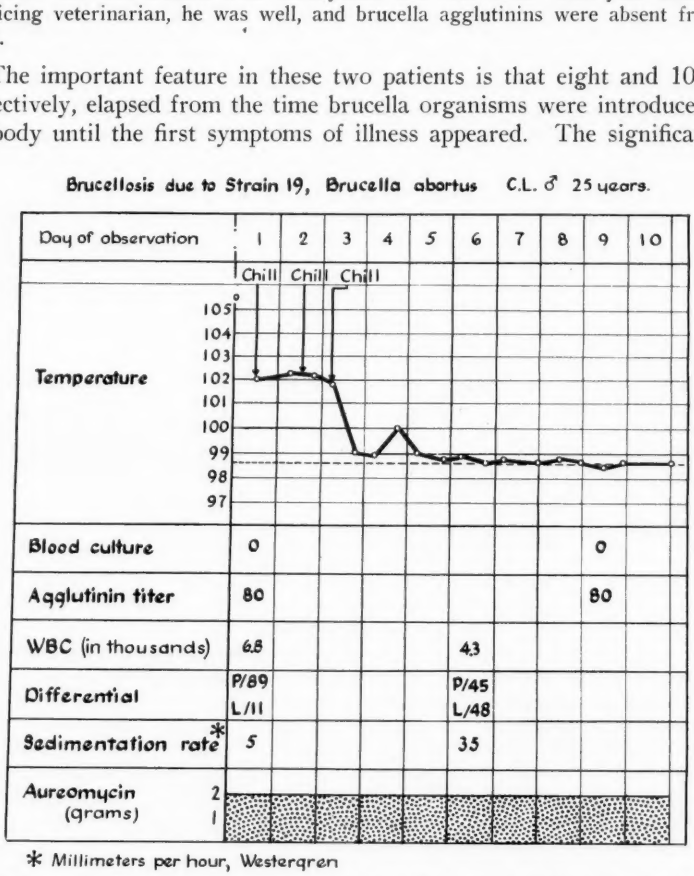


FIG. 3. The clinical course of a veterinarian with acute brucellosis who accidentally inoculated his hand with strain 19. He had had brucellosis previously, and became ill within six hours of the accident. (From "Human brucellosis caused by *Brucella abortus*, strain 19," W. W. Spink and H. Thompson, J. A. M. A. **153**: 1162 (Nov. 28) 1953; reproduced by permission.)

this period of incubation in the pathogenesis of brucellosis will be discussed shortly. If guinea pigs are infected experimentally with brucellae, five to seven days must elapse before the animals display intradermal sensitivity to brucella antigen. By this time brucellae are well localized intracellularly in the tissues of the reticuloendothelial system. Another related aspect of experimental brucellosis is that animals can be infected most effectively by introducing the organisms into the conjunctivae.

The course of illness in two men who had both historical and immunologic evidence of having had brucellosis prior to being accidentally infected with strain 19 Br. abortus.

Case 3. This patient's illness has been reported in detail,[2] but the essential features are as follows: A 25 year old white veterinarian, while engaged in vaccinating cattle with strain 19, accidentally introduced the needle attached to a syringe containing strain 19 into the palm of his right hand. Within six hours the hand became swollen, painful and tender, and chills and fever developed. Ten hours after the accident he medicated himself with chlortetracycline. His course is depicted in figure 3. Twenty-four hours after the accident he was quite toxic. His temperature

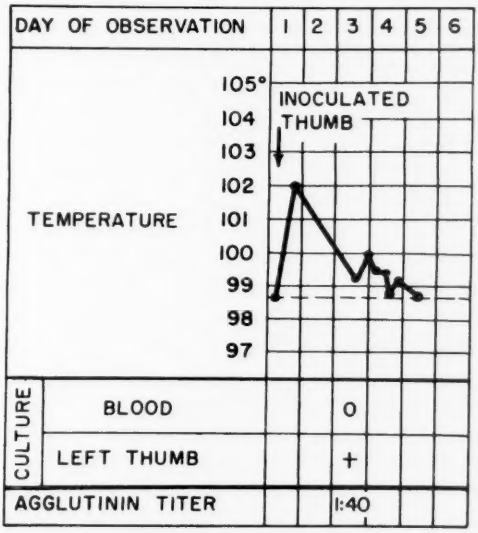


FIG. 4. Clinical course of a veterinarian who accidentally inoculated his thumb with strain 19. The thumb became painful and swollen within 30 minutes of the accident, and within a few hours he developed chills and fever. Strain 19 was cultured from the puncture site of the thumb. (From "The nature of brucellosis," W. W. Spink, 1956, University of Minnesota Press, Minneapolis, p. 142.)

was 102° F. His right hand was swollen and tender, lymphangitis was present, and the right axillary lymph nodes were enlarged and tender. Blood cultures remained sterile, but brucella agglutinins were present in a titer of 1 to 80. He recovered promptly. Although strain 19 was not isolated from the blood or tissues of this patient, there is little reason to doubt that this strain was responsible for his last illness.

It is noteworthy that this man had previously introduced strain 19 into his foot in an accidental manner, and had had immediate localized and systemic reactions. He was known to have been infected with brucellae before this previous accidental infection. Furthermore, brucella agglutinins had been demonstrated repeatedly in his blood prior to his last accident.

Case 4. A 30 year old white veterinarian, while occupied in vaccinating cattle with strain 19, accidentally introduced the needle into his left thumb. *Within 30*

minutes the thumb became swollen and painful. Within a few hours the hand became swollen, lymphangitis of the arm appeared, and a tender left axillary lymph node was detected. On the evening of the day of the accident he developed nausea, vomiting, chills, sweats, and a temperature of 102° F. His clinical chart is reproduced in figure 4. Forty-eight hours after the accident he felt improved without the benefit of antibiotic therapy. At this time the left thumb was still swollen, red and painful, with a small fluctuant area present at the site where the needle had been inserted. A drop of purulent material was expressed from the left thumb, from which strain 19 was isolated. A culture of blood remained sterile, and the brucella agglutinin titer was 1 to 40. He recovered by the fifth day, and he has remained well.

A pertinent feature in this patient's illness was that he had been exposed to brucellosis previously, and he was known to have had brucella agglutinins in his blood for at least three years prior to his accident.

In summary, then, four veterinarians accidentally inoculated themselves with living organisms of strain 19 *Br. abortus.* Two of these individuals had had neither historical nor immunologic evidence of brucellosis prior to their accident. Following a rather heavy inoculum of organism into the conjunctivae of these two persons, no signs of ill health appeared for several days, and then a systemic febrile illness was manifested, which proved to be brucellosis. In contrast, two other men accidentally inoculated themselves through the skin with strain 19. Within a few hours severe localized and systemic reactions ensued. Both of these individuals had been infected before with brucellae, and both had accelerated reactions due to the previously acquired brucella hypersensitivity. Although the two individuals with delayed illness were infected following introduction of the organisms into the eyes, and the two persons with immediate sickness were infected through the skin, this difference in the primary sites of infection was unrelated to the immediate course of events. The immediate or delayed systemic reactions were dependent upon the presence or absence of brucella hypersensitivity at the time of infection.

A Concept of the Genesis of Acute Human Brucellosis Involving Bacterial Hypersensitivity

As has already been pointed out, many students of brucellosis have looked upon acquired brucella hypersensitivity as a major contributing factor in the illness of persons having chronic brucellosis. Patients with a prolonged illness often display an exquisite sensitivity to brucella antigens. It has also been recognized that individuals convalescing from an acute attack of brucellosis, or those who have recovered completely, will very frequently manifest marked dermal sensitivity to brucella antigens. This acquired hypersensitivity can endure for many years. In fact, a febrile illness compatible with brucellosis can be provoked in otherwise healthy but sensitized individuals following the injection of brucella antigen. We have accumulated evidence that attacks of illness which were interpreted as relapses of

brucellosis were induced by highly sensitized individuals coming into contact with nonviable brucella antigen.

The course of the illness in the four veterinarians cited in this report suggests some analogies to serum sickness. Exposure of the human host to horse serum for the first time requires a latent period of several days before the onset of symptoms, although, as is the case with brucellosis, some persons may be sensitized without symptoms, or sensitization may be minimal and of no clinical significance. Repeated exposure of a patient sensitized to serum causes an accelerated systemic reaction with a very short latent period, such as in the reinfected veterinarians who had been previously exposed and sensitized to brucella antigen. It must be emphasized, however, that acquired hypersensitivity of the delayed-tuberculin type is most significant in brucellosis, whereas in serum sickness the sensitized individual can also exhibit the immediate type of anaphylactic reaction which is associated with circulating or humoral antibody.

Objective evidence of acquired brucella hypersensitivity can be demonstrated during the acute illness by means of a skin test with brucella antigen, and by an exaggeration of the symptoms when the antigen is introduced into the blood. It has not been easy to demonstrate in man that inflammatory reactions in tissues other than in the skin may be accelerated during the acute illness because of acquired hypersensitivity. But Dr. A. I. Braude made a unique observation in our clinic that contributes further to the understanding of hypersensitivity in acute brucellosis. He observed a 19 year old man who had acute brucellosis. *Br. abortus* was isolated from the blood on two occasions. He introduced brucella antigen intradermally into this sensitized person, and within a few hours a severe localized reaction appeared, along with chills and an accentuation of his fever. Forty-eight hours after the tests had been applied the patient manifested jaundice. A hepatic biopsy revealed an extensive inflammatory reaction with many granulomas. The jaundice subsided within a week, and a second liver biopsy, 16 days after the first, revealed considerably less inflammation, with only an occasional granuloma present. Jaundice is rare in acute brucellosis, although the appearance of hepatic granulomas is common.[5] It was concluded from this observation that the hepatic inflammation was enhanced in a sensitized patient by the brucella antigen.

The significance of hypersensitivity in the host-parasite relationship in brucellosis can be appreciated more clearly if a brief review is given on the fate of brucellae immediately after entrance of the bacteria into the body. When brucellae are introduced into the skin of a guinea pig there is an immediate mobilization of polymorphonuclear leukocytes, and then macrophages, at the site of inoculation. The surviving brucellae pass quickly into the lymphatics, reaching the regional lymph nodes. Phagocytosis and destruction of brucella occur in the nodes, but bacterial proliferation can also take place, and then the blood stream is invaded. Further antibacterial

factors operate in the blood with lysis of the brucellae and the liberation of brucella endotoxin. The significance of endotoxin in the pathogenesis of brucellosis and its relation to hypersensitivity will be discussed shortly. Organisms that survive the barrier of the blood-defense mechanism localize intracellularly within the liver, spleen, lymph nodes and bone marrow. Brucellae may be destroyed in these areas, or multiplication can take place, with reinvasion of adjacent cells and also of the blood stream. It has been shown experimentally in our laboratory how quickly brucellae can be demonstrated within the sinusoids of the liver after primary entrance into the host.[6] The elapsed time was only a few hours. The latent or incubation period is concerned not only with the distribution and proliferation of brucellae, but during this time sensitization of the tissues to brucella antigen

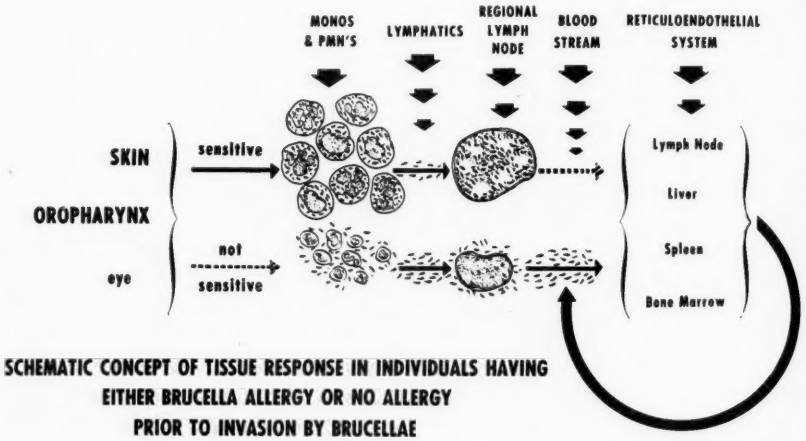


FIG. 5.

also occurs. The host may or may not exhibit symptoms of brucellosis shortly following invasion of the tissues. The incubation period can extend for weeks or months before illness occurs.[5] This long delay in the appearance of symptoms is not unique for brucellosis.

In the experimental animal, or in man, when reinfection occurs with brucellae, an explosive inflammatory reaction takes place at the portal of entry. Arias-Stella [7] has shown that if brucellae are introduced into the skin of a previously infected guinea pig, an accelerated, local inflammatory reaction occurs in which macrophages phagocytize and destroy the organisms. Likewise, when Burnet [8] reinfected guinea pigs intraperitoneally with brucellae, an intense inflammation occurred in the cavity, and phagocytosis and destruction of the brucellae took place. Burnet also reproduced in himself the sequence of events that have just been described in the two veterinarians who had been previously infected and strain 19 was then ac-

cidentally inoculated into their subcutaneous tissue. Burnet had recovered from a severe attack of brucellosis due to *Br. melitensis*. He then introduced viable organisms of the same species into his skin. This was followed shortly by an inflammatory response at the site of inoculation, along with lymphangitis and lymphadenopathy. He cultured *Br. melitensis* from the localized skin abscess 20 days later. Burnet concluded that he had reproduced in himself Koch's phenomenon for brucellosis.

In summary, our present knowledge of the sequence of events in brucellosis following primary infection and those following reinfection can be schematically presented as in figure 5. It will be noted that, regardless of the portal of entry of the organisms, brucellosis involves primarily the lymphatic system during the very early stages of the disease. In the patient who has had a previous exposure to brucellosis, active phagocytosis and destruction of the brucellae occur at the site of invasion or in the regional lymph nodes. This is associated with considerable local inflammatory reaction, which simulates Koch's phenomenon in tuberculosis. In the sensitized individual, it is not unlikely that systemic manifestations occur even though living bacteria do not invade the blood stream. Nonviable, antigenic products circulating in the blood in very minute quantities are sufficient to produce symptoms. The nonsensitive individual may have invasion of the blood stream *without* symptoms, and even though various organs are parasitized, illness may not occur, or may be delayed for a long period of time. Experimental studies have shown that brucellae can localize intracellularly for many months without causing objective evidence of illness. It is apparent that the degree of hypersensitivity will have a direct bearing on whether symptoms will occur early after invasion of the body by brucellae.

The concept that the immediate or delayed appearance of symptoms is related to tissue hypersensitivity is supported further by referring to the reports of other cases of human infection caused by strain 19. In the patient reported by Gilman,[1] organisms of strain 19 were accidentally introduced into the eye, and 16 days elapsed before the first symptoms appeared. This person was also a student of veterinary medicine. The report of Sadusk et al.[4] involved a physician who accidentally inoculated both eyes with strain 19 while vaccinating cattle. Thirty-one days elapsed before the first symptoms were noted. Serial serologic studies were made on this patient. At the time of the accident both the brucella agglutination and complement fixation tests were negative, but significant titers were observed 45 days later. The patient reported by Bardenwerper[3] was a veterinarian known to have been infected by brucellae prior to injecting organisms of strain 19 accidentally into his hand. Within a few hours this individual had a painful and swollen hand, and eight hours after the accident he had chills, a fever of 102° F., headache, myalgia and arthralgia. We have had detailed communications from two veterinarians who had had repeated exposure to infected cattle, and who had had brucellosis prior to inoculating themselves

accidentally in the hand with organisms of strain 19. In both instances, *immediate* and severe illness occurred. Although no information is available on the subject, it could be assumed that if a sensitive individual were to introduce brucellae into the conjunctivae, immediate and severe inflammation of the ocular tissues might very well ensue.

The Significance of Endotoxin in the Pathogenesis of Brucellosis and Its Relation to Hypersensitivity

A common feature of Gram-negative bacteria is the presence of a lipoprotein-carbohydrate complex on or near the cell surface of smooth cultures. The carbohydrate component is very likely the toxic factor of this somatic endotoxin. The physiologic and toxic effects of brucella endotoxin are similar to those induced by the endotoxins of other Gram-negative organisms.

We have studied the biologic activity of brucella endotoxin intensively, and we have concluded that it plays a major rôle in the illness caused by brucellae. Interest in the significance of brucella endotoxin was first aroused in 1948 when critically ill patients having brucellosis due to *Br. melitensis* were treated with chlortetracycline.[9] Within eight to 12 hours of the initial dose of the antibiotic, one-half of the patients treated exhibited an alarming clinical picture bordering on shock in which there was a drop in blood pressure, tachycardia, and an abrupt rise in fever. It was postulated that these undesirable effects of therapy were due to the antibacterial activity of the antibiotic, which liberated toxic somatic material from the bacteria. It was of interest to observe later that the somatic endotoxin of the most invasive strains of *Br. melitensis* was no more toxic for mice than the endotoxin extracted from strain 19 *Br. abortus*.[10] From these observations the thesis was developed that if organisms could multiply in the human host, brucellae of strain 19 should cause as severe a disease as that due to *Br. melitensis*, because of the liberation of an endotoxin, which in itself was toxic, and because of acquired hypersensitivity to the endotoxin. Subsequent clinical observations, including the present report, have supported this thesis.[2, 11] While brucella endotoxin is quite toxic for human beings in general, it is remarkable what a severe degree of hypersensitivity patients can exhibit to the endotoxin during the acute illness or after recovery. Abernathy [12] has made a direct correlation between the toxicity of endotoxin when given intravenously and the results of the skin reaction produced by brucellergen or purified protein brucellae. Persons displaying marked dermal hypersensitivity had severe systemic reactions from corresponding small amounts of endotoxin given intravenously. Similar observations have been made by others.[13]

Although acquired hypersensitivity to brucella endotoxin offers a partial explanation for illness in the majority of patients with active brucellosis, there still remains the occasional patient who has a severe attack of acute brucellosis but in whom skin tests with brucella antigen remain negative,

revealing a state of anergy. A comparable state is seen in the patient with miliary tuberculosis and his failure to react to tuberculin. The critically ill patient with brucellosis and negative skin tests is usually heavily infected, and a bacteremia is demonstrable. The severity of the symptoms in these patients can be related to the diffuse inflammatory disease present in the tissues and its resultant metabolic or biologic effects, and to the relatively large amounts of endotoxin liberated from the organisms through the bactericidal action of blood and the tissues. Hall [14] has demonstrated the marked bactericidal action of blood in patients with acute brucellosis. As these patients improve and the infection is brought under control, dermal hypersensitivity becomes apparent.

A general characteristic of endotoxin from Gram-negative bacteria is the tolerance to endotoxin that is produced in animals after an initial injection of the material. Mice will tolerate lethal doses of brucella endotoxin following inoculation with sublethal doses.[15] We have also demonstrated that brucella endotoxin offers mice protection against viable brucellae. It is now generally accepted that a relative immunity against reinfection with brucellae is established in animals and in man following infection.[5] However, chronically infected mice have been found to be less tolerant to endotoxin than are uninfected control animals. It has been concluded that this reduction in tolerance to endotoxin during the course of the infection is due to the establishment of hypersensitivity to brucella antigen.

The undesirable effects of brucella endotoxin, including those induced by acquired hypersensitivity, can be subdued by adrenocorticosteroids and corticotropin. Cortisone protects intact mice against lethal doses of endotoxin.[10] We have also found that hydrocortisone, 9 alpha-fluorohydrocortisone, as well as aldosterone, will protect adrenalectomized mice against brucella endotoxin.[16] Similarly, chlorpromazine protects intact and adrenalectomized mice against lethal doses of brucella endotoxin.[16] It was demonstrated further that the administration of corticotropin to patients acutely ill with brucellosis resulted in prompt improvement.[17] Important to the present discussion, dermal hypersensitivity to brucella antigen was also suppressed by the hormone. Similar clinical results have been obtained with cortisone, hydrocortisone and prednisone. Adrenocorticosteroids will prevent the systemic reactions in hypersensitive patients when brucella endotoxin is introduced intravenously, and the reactions promptly subside when the steroids are administered after the introduction of endotoxin into sensitized persons.

The Public Health Aspects of Strain 19, *Brucella abortus*

There is substantial evidence that calfhood vaccination with strain 19 does afford cattle partial protection against the more invasive strains of *Br. abortus*. Chronic disease in cattle is not established by strain 19, and

there is no known instance that human brucellosis due to this strain has had its origin from immunized cattle.

In view of the success that has been attained in cattle with strain 19, it has been suggested from time to time that this vaccine should be used for immunizing human beings who are heavily exposed in certain occupations to highly invasive strains of *Br. melitensis.* Recent information reaching the World Health Organization in Geneva points out that Russian workers have investigated this problem, and as a result thousands of Russian people whose daily occupations bring them into contact with areas heavily contaminated with *Br. melitensis* have been vaccinated with living organisms of strain 19 *Br. abortus.* Coincident with human immunization, the attack rate of brucellosis has been reported to have diminished sharply. On the basis of the information available, it would not be sound to pass judgment on the merits of this immunization program. Experimental results and field trials in animals with strain 19 in attempts to demonstrate protection against *Br. melitensis* do not support the apparent protection obtained by human beings in Russia. Strain 19 will protect guinea pigs against infection with *Br. abortus,* but not against the more invasive strains of *Br. melitensis.* But more important is the fact that the natural reservoirs for *Br. melitensis* are in sheep and goats, and strain 19 does not protect susceptible animals of these species against *Br. melitensis.*

As far as the United States is concerned, there is no justification for employing strain 19 for human immunization. In the first place, although strain 19 does have attenuated virulence, an occasional person might suffer ill effects, as this report has emphasized. Second, most of the human brucellosis in this country is caused by *Br. abortus,* and this species, in general, causes much less severe disease than that caused by *Br. melitensis.* And third, brucellosis is not primarily a human disease. The reservoir resides in domestic animals, particularly in cattle. The incidence of human brucellosis in the United States is diminishing rapidly because milk for human consumption is almost universally pasteurized, and because the reservoir of the disease in cattle is being successfully eradicated.

Summary

1. Strain 19, a stable variant of *Br. abortus,* with effective antigenic properties and having attenuated virulence, is being used extensively for immunizing cattle. Human infections due to strain 19 rarely occur. In this report the clinical and immunologic data are presented on four veterinarians who were accidentally infected while immunizing cattle.

2. Two of the veterinarians infected with strain 19 had never had brucellosis previously, and a latent or incubation period of several days elapsed before symptoms of the disease appeared. On the other hand, two of the veterinarians had been infected before and within a few hours became

acutely ill. It is concluded that acquired brucella hypersensitivity plays a significant rôle in the genesis of the illness of acute brucellosis.

3. Additional experimental and clinical studies are cited relative to the significance of brucella endotoxin in acute brucellosis and its relation to acquired hypersensitivity.

4. Although immunizing cattle with strain 19 *Br. abortus* has expedited the eradication of bovine brucellosis in the United States, there is no justification for employing this vaccine for human immunization programs in this country.

Summario in Interlingua

Racia 19 es un variante stabile de *Brucella abortus,* con efficace proprietates antigenic e un virulentia attenuate. Illo es usate extensemente pro immunisar bestial contra brucellosis. In humanos, infectiones per racia 19 es rar. Le presente reporto concerne le datos clinic e immunologic del casos de quatro veterinarios qui esseva inficite accidentalmente durante le labor de immunisar animales. Duo del veterinarios inficite con racia 19 non habeva habite brucellosis unquam previemente, e un periodo de latentia o de incubation de plure dies passava ante que symptomas del morbo deveniva manifeste. Tamen, le duo altere veterinarios habeva habite previe infectiones, e intra alicun horas post inficer se accidentalmente con racia 19 illes deveniva acutemente malade. Le observationes in iste casos monstra que le acquisition de hypersensibilitate a brucella ha un rolo significative in le genese de brucellosis acute. Altere studios effectuate in nostre laboratorio e in nostre clinica es citate pro monstrar que endotoxina de brucella ha un rolo significative in le genese de brucellosis tanto acute como etiam chronic. Le genese del reaction a endotoxina es clarmente relationate al acquirite hypersensibilitate a ille endotoxina. Finalmente, ben que le immunisation de bestial per medio de racia 19 de *Br. abortus* ha essite de valor in eradicar brucellosis bovin in le Statos Unite, le empleo de iste vaccino in programmas de immunisation human non es justificate in iste pais.

BIBLIOGRAPHY

1. Gilman, H. L.: Undulant fever caused by *Brucella abortus,* strain 19, Cornell Vet. **34**: 193, 1944.
2. Spink, W. W., and Thompson, H.: Human brucellosis caused by *Brucella abortus,* strain 19, J. A. M. A. **153**: 1162, 1953.
3. Bardenwerper, H. W.: Human sickness caused by *Brucella abortus,* strain 19, J. A. M. A. **155**: 970, 1954.
4. Sadusk, J. F., Jr., Browne, A. S., and Born, J. L.: Human brucellosis resulting from *Brucella abortus* strain 19 vaccine, J. A. M. A. **164**: 1325, 1957.
5. Spink, W. W.: The nature of brucellosis, 1956, University of Minnesota Press, Minneapolis, p. 185.
6. Braude, A. I.: Studies in the pathology and pathogenesis of experimental brucellosis. II. The formation of the hepatic granuloma and its evolution, J. Infect. Dis. **89**: 87, 1951.
7. Arias, J.: Contribucion al conocimiento de la pathologia de la brucelosis, An. Fac. med., Lima **34**: 429, 1951.
8. Burnet, E.: Des reinoculations dans l'infection a M. melitensis, en particulier d'apres la maladie experimentale du cobaye, Arch. Inst. Pasteur de Tunis **14**: 62, 1925.
9. Spink, W. W., Braude, A. I., Castaneda, M. R., and Goytia, R. S.: Aureomycin therapy in human brucellosis due to *Brucella melitensis,* J. A. M. A. **138**: 1145, 1948.

10. Spink, W. W., and Anderson, D.: Experimental studies on the significance of endotoxin in the pathogenesis of brucellosis, J. Clin. Investigation **33**: 540, 1954.
11. Spink, W. W.: The significance of endotoxin in brucellosis: experimental and clinical studies, Tr. A. Am. Physicians **67**: 283, 1954.
12. Abernathy, R.: Sensitivity of human subjects to Brucella endotoxin and its significance in the pathogenesis of brucellosis, J. Lab. and Clin. Med. **48**: 780, 1956.
13. Pirosky, I., and Molinelli, E. A.: Estudios sobre alergia brucelosa. I. Empleo del complejo glucidolipido de brucella en la investigacion alergica del hombre, Revist. de Med. y Cienc. afines, Buenos Aires **6**: 850, 1944.
14. Hall, W. H.: The bactericidal action of human blood against Brucella and its specific inhibition, *in* Third Inter-American Congress on Brucellosis, Washington, D. C., Pan American Sanitary Bureau, 1950, p. 87.
15. Abernathy, R. S., and Spink, W. W.: Protection against Brucella with heterologous endotoxins, J. Clin. Investigation **35**: 687, 1956.
16. Halberg, F., Spink, W. W., and Bittner, J. J.: Protection by aldosterone and 11,17-oxycorticoids against effects of Brucella somatic antigen in adrenalectomized mice, Endocrinology **59**: 380, 1956.
17. Abernathy, R. S., Halberg, F., and Spink, W. W.: Studies on the mechanism of chlorpromazine protection against Brucella endotoxin in mice, J. Lab. and Clin. Med. **49**: 708, 1957.
18. Spink, W. W., and Hall, W. H.: The influence of cortisone and adrenocorticotrophic hormone on brucellosis. II. Adrenocorticotrophic hormone (ACTH) in acute and chronic human brucellosis, J. Clin. Investigation **31**: 958, 1952.

REGIONAL ENTERITIS: AN EVALUATION OF THE PRESENT-DAY THERAPEUTIC MANAGEMENT *

By J. Arnold Bargen, M.D., F.A.C.P., *Rochester, Minnesota*

Introduction

Much has been said and written about regional enteritis in the last few years. On the basis of description, it is a comparatively new entity, for an accurate characterization of it did not exist until Crohn and his associates defined it decisively in 1932. Thus, from a period early in our century up to the present, there have been an impressive accumulation of information about regional enteritis and an extensive collection of data concerning patients with the disease. One of the problems remaining is adequate evaluation of our information to date.

Regional enteritis attacks mainly young adult persons. It is typified clinically by abdominal cramps, diarrhea, fever, loss of weight, anemia and the formation of abdominal and perianal abscesses and fistulas. The disease may, however, affect persons at any time of life, even in the declining years. Moreover, while it is true that the lesions of regional enteritis usually are limited in both the initial and the recurrent stages to the terminal portion of the small intestine, the disease actually may involve any portion of the small intestine, from the duodenum to the cecum, in one manifestation or another. In fact, regional enteritis sometimes may encroach upon the large intestine.

What was called, in the early days, "terminal ileitis," long since has been given the designation of "regional enteritis," a term which indicates involvement of any segment of small intestine. The fact that this disease is truly regional becomes particularly impressive when we consider how frequently it recurs, and then extends, after surgical resection of the diseased segment of bowel. As a rule, the site of earliest recurrence is the ileocolic anastomosis. Here the recurrent process generally remains limited to that part of the small bowel proximal to the site of anastomosis, and the extension is orad rather than caudad.

I find that at the Mayo Clinic we began to speak of this disease in 1912, and that between 1912 and 1921, about once each year, we made a diagnosis

* Presented at the Thirty-eighth Annual Session of The American College of Physicians, Boston, Massachusetts, April 11, 1957.

From the Section of Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

Requests for reprints should be addressed to Section of Publications, Mayo Clinic, Rochester, Minnesota.

which later very likely would have been regarded as that of regional enteritis.

Then we saw that the incidence of this disease gradually began to increase. In the year 1931 the diagnosis of regional enteritis was made nine times. In the years from 1941 to 1949, the diagnosis was made an average of 40 times each year, and in a single year the maximal number of patients seen was 55. This figure of course refers to new patients only. During the years between 1912 and 1949 the diagnosis of regional enteritis was made for 600 patients. Our records show that in two patients the disease began at the age of four years, and that in 336 of the 600 patients it occurred between the ages of 16 and 30 years. In three patients regional enteritis began between the ages of 70 and 74 years. On the other hand, the disease began after the age of 50 years in only 36 instances. These facts, and the nature of the disease, with its relentless progression and the high rate of postoperative recurrence, make a reëvaluation of current methods of therapy of considerable importance to our future therapeutic approach.

Present-Day Treatment

In the early days of acceptance of regional enteritis as an entity, the internist and gastroenterologist were primarily concerned with recognition and diagnosis of the disease. Once the diagnosis was established, surgical consultation was sought, and very likely surgical resection of the involved portion of bowel in one or several stages was undertaken.

The next development was the technic of exclusion, in which the disease process was excluded from the intestinal continuity by performance of ileocolic anastomosis, leaving the diseased segment of bowel in the abdomen undisturbed. Obviously, use of this technic was a tacit admission that the earlier procedure of resection of the diseased portion of bowel left much to be desired, and all too frequently was not a curative operation.

Gradually, as surgical experience with this disease broadened, there developed a realization that not all of these patients presented surgical problems. The result is that currently we have become very conservative in respect to the treatment of regional enteritis. The usual patient who has regional enteritis is now treated medically. Still, it must be allowed that at best the treatment of this disease is not remarkably satisfactory.

Yet a number of measures have been found to be helpful in the management and control of this stubborn condition, as I shall explain. First, however, we must accept the fact that patients who have regional enteritis can be divided into two main categories: those who do not have complications, and those who do. Fistulas and abscesses in the abdomen, perforation, obstruction and the forming of large masses constitute undebatable surgical problems, but even when complicating conditions have been corrected and the diseased segment of bowel has been removed, the disease still has a tendency to recur.

The situation is further complicated by the fact that several types of patients in various stages of this disease constitute medical problems. For instance, the patient in whom a relatively short segment of bowel is involved by enteritis which obviously is of the ulcerative rather than the hyperplastic type, and whose disease remains fairly stationary for some time, should be treated medically. Another substantial group of patients includes those whose disease is much too extensive for an attempt at surgical resection. In these patients many segments of bowel are involved, with uninvolved areas between, and the involvement is situated high in the jejunum and duodenum. Secondary deficiency problems develop in such patients, and they may be victims of profound anemia, disturbance of growth and development, secondary arthritis, uveitis and pyoderma. These patients, it must be admitted, are poor candidates for any form of therapy, but they certainly cannot be improved by any surgical procedure.

A third type of patient who becomes a problem of the internist is the one who has undergone resection several times, who is experiencing further recurrence of the disease, and who now implores your help.

The Patient Without Complications: Earlier I spoke of the two main categories of patients. Those in the first category—those who do not have complications—frequently improve strikingly as a result of the following regimen. The condition must be thoroughly discussed with the patient. The nature and chronicity of the disease, the possible outlook and the ultimate prognosis and the reasons for medical therapy should be outlined. The treatment should be similar to that of any chronic debilitating infection, with certain specific modifications designed for and applicable to this particular condition. The diet should be very high in proteins, and free of fiber and irritants. Rest, both physical and emotional, is of considerable importance. Such drugs as salicylazosulfapyridine (Azulfidine), administered as in ulcerative colitis, have been helpful to an appreciable number of patients with uncomplicated regional enteritis. Many of them have an inordinate amount of discomfort and abdominal cramps. The management of these sometimes taxes the most resourceful of physicians. Very likely the properties of some of the tranquilizing drugs may solicit favor. Narcotic agents should be avoided because of the chronicity of the disease, although at times it may be necessary to resort to agents which have low addictive properties, such as levorphan tartrate (levo-dromoran tartrate).

The most important therapeutic adjunct in the treatment of this group of patients has been roentgen therapy judiciously applied. At first thought, the comparatively light roentgen therapy which we have employed might seem to be scarcely more effective than a placebo, but we have now administered it to more than 150 patients, and a large number of them have reported substantial improvement. In fact, in a few the roentgenograms disclose a return to normal. In some patients obstruction has developed

after several courses of roentgen therapy, but when surgical exploration became advisable later on, healing of the disease was noted at that time.

Roentgen therapy is administered in courses. The anterior part of the abdomen is divided into four fields, each about 15 by 15 cm. One field is treated each day with a dose of 150 r, the course of treatment for the four fields thus requiring four days. The technical factors employed are 250 KV at a distance of 50 cm., with a half-value layer of 1 to 2 mm. of copper. Three such courses are administered to each patient a month apart. Subsequently, treatment is repeated on the basis of the clinical findings.

The Patient With Complications: The second main group of patients includes those who have complications, such as profound anemia, deficiency states and other systemic disturbances. Members of this group constitute a far more difficult problem. In general, they too will be benefited by the program I outlined. In addition, it frequently is necessary to administer blood repeatedly. Attention must be paid to the marked deficiency states which sometimes supervene, and to the avitaminosis which develops. Yet the deficiency state is not always secondary to the extensive disease, because we have seen deficiency states in patients with a relatively small portion of bowel involved by the enteritis.

The administration of blood probably is one of the major therapeutic measures available in this group of patients. One young man came to our attention because he had extensive recurrent disease, and had received so many infusions of blood that he had established his own blood bank. By the time we first saw him he had received more than 500 pints of blood.

Use of Steroids: Steroids have a limited field of usefulness in the therapy of regional enteritis. In the average instance of the disease one might say that the use of steroids actually is contraindicated because of the difficulties they frequently present while they are being administered. Massive hemorrhage and intestinal perforation have occurred during the active administration of these hormones. Furthermore, the favorable effects obtained from steroids in some of these cases have been only temporary.

It is still true, however, that among patients with the secondary deficiency syndrome resembling sprue, steroids, judiciously administered, may bring about a marked favorable change. The same can be said of the use of steroids in secondary uveitis, arthritis and pyoderma. But the steroids in any form should be given only after careful consideration of each patient.

Recurrence and Survival: Recurrence rates after surgery among patients who have regional enteritis are high. On the other hand, survival rates likewise are high. The 10-year survival rate after the diagnosis of regional enteritis had been made at the Mayo Clinic was 81.1%, and most of the patients were doing very well. Thus, the prospects for survival in the face of this disease are encouraging. This fact by itself should quicken our efforts toward improving the therapy for these patients.

Comment and Summary

When the type of treatment to be administered to any given patient with regional enteritis is being considered, several facts must be kept in mind. First, regional enteritis is a disease of young adult persons. Second, recurrences of the disease after resection and extension of the disease without resection are likely. Third, the incidence of these recurrences is much greater among younger persons. Among the 36 patients whose disease began after the age of 50 years, only four experienced recurrences later in life. Fourth, certain complications are definitely surgical problems, and must be so considered from the start. Fifth, although the measures currently available to us leave much to be desired, they have been very satisfactory in many cases, and the situation is by no means devoid of promise. We have maintained large numbers of patients with this disease in a satisfactory state of health, so that they have been able to carry on their usual occupations and living activities. Moreover, in some instances complete regression of the disease has occurred.

Summario in Interlingua

Le hodierne therapia de enteritis regional es discutite super le base de 600 casos vidite al Clinica Mayo inter 1912 e 1949. Le morbo occurre principalmente in juvene adultos, sed illo es etiam incontrate—multo plus rarmente—in phases avantiate del vita o durante le pueritia. Ab le puncto de vista clinic le morbo es characterisate per crampos abdominal, diarrhea, febre, perdita de peso, anemia, e le formation de abscessos e fistulas abdominal e perianal. Le experientia ha demonstrate que le resection chirurgic del areas afficite non representa un garantia de sanation. Recurrentias es frequente. Anastomose ileocolic, effectuate sin disturbation del morbide segmento del intestino, ha frequentemente essite sequite per recurrentia al sito del anastomose. Gradualmente un plus conservative methodologia se ha disveloppate. Le usual patiente con enteritis regional es nunc tractate con medios medical. Reposo (tanto physic como etiam emotional), non-irritante dietas a alte contento proteinic, therapia specific pro problemas de deficientia, tractamento de anemia (specialmente per transfusiones)—omne istos es mesuras que ha provate lor valor. Leve cursos de radiotherapia abdominal ha essite usate in plus que 150 casos, e un grande numero del patientes ha reportate grados considerabile de melioration. Steroides ha apparentemente un restringite campo de ultitate. Fistulas e abscessos abdominal, perforation, obstruction, e le formation de grande massas es ancora sin dubita grave problemas chirurgic. Ben que extension del morbo e recurrentia post-chirurgic es multo commun, specialmente in juvene patientes, e ben que le procentage del curas es basse, un certe mesura de optimismo es justificate per le alte procentage de superviventes. Al Clinica Mayo, isto amontava in dece annos a 81,1%, e multe patientes se mantene in un satisfacente stato de sanitate.

LONG-TERM FOLLOW-UP OF PATIENTS WITH HEALED BACTERIAL ENDOCARDITIS *

By Buford Hall, M.D., *Chicago, Illinois*

The subsequent course of patients who are able to leave the hospital after bacteriologic cure of bacterial endocarditis has aroused considerable interest and some controversy, although relatively little published data exist. Most reports are concerned with a short period of follow-up of a few months to one year. The present study was undertaken in an attempt to provide more data on the long-term prognosis of patients with healed endocarditis.

Methods and Results

During the seven years 1944 through 1950, 32 patients with bacterial endocarditis were admitted to the University of Illinois Research and Educational Hospitals. Some of the diagnostic and therapeutic features of these cases, as well as others more recently treated, are described in a recent review.[1] The diagnosis was established in each case by positive blood cultures in the presence of the usual clinical picture, or by necropsy. All patients received penicillin for at least 48 hours. Fifteen of these 32 patients died during the initial hospitalization of uncontrolled infection, congestive heart failure, or other complications of the disease. Several of these deaths occurred during or following inadequate therapy at a time when penicillin was in short supply.

Seventeen patients were discharged from the hospital, at which time they were considered to be bacteriologically cured of their disease. Each patient was followed to the present time or to death. The minimal follow-up period for the living patients was six years, the maximal, 10 years. The mean durations of follow-up for dead patients, living patients, and all patients were 1.6 years, eight years, and 5.4 years, respectively. Data on these 17 patients are presented in table 1.

There were 11 females and six males. The mean age of all patients was 34.2 years, with a range of 13 to 56 years.

In 14 of the patients an alpha streptococcus was isolated from the blood stream, and in 12 of these the organism was inhibited by 0.25 unit or less of penicillin per milliliter. Sensitivity of the organism was not determined in two. In two other patients repeated blood cultures were negative, and bacterial endocarditis was proved at necropsy performed six and seven

Table 1

Clinical and Laboratory Data on 17 Patients with Healed Bacterial Endocarditis

* Received for publication March 29, 1957.

From the Department of Medicine, University of Illinois College of Medicine, and Research and Educational Hospitals, Chicago, Illinois.

Requests for reprints should be addressed to Buford Hall, M.D., Assistant Professor of Medicine, University of Illinois College of Medicine, 840 South Wood Street, Chicago 12, Illinois.

TABLE 1

Clinical and Laboratory Data on 17 Patients with Healed Bacterial Endocarditis

Case No. Hospital No.	Sex and Age at Time of Therapy	Date Therapy Stopped	A.H.A.* Functional Capacity at Discharge	Duration of Follow-Up (in Months)	A.H.A.* Functional Capacity at Follow-Up	Underlying Cardiovascular Disease	Cause of Death	Infecting Organism, and Its Sensitivity† to Penicillin	Duration of Therapy	Total Dosage of Penicillin (in Millions of Units)	Duration of Symptoms Prior to Final Therapy	Cardiac Enlargement at Beginning of Therapy
1 314175	F 51	6-18-46	Class IV	6	Dead	RHD, MR, AR‡	Congestive heart failure	Alpha streptococcus; not done	97 days	47	12 weeks	None
2 317940	F 18	7-22-46	Class I	119	Class I	RHD, MR, MS		Alpha streptococcus; 0.25	31 days	11.7	8 weeks	Slight
3 318580	F 26	8-29-46	Class I	12	Dead	RHD, MR	Pulmonary tuberculosis	Alpha streptococcus; 0.25	45 days	22.2	104 weeks	None
4 319763	M 56	9-23-46	Class I	117	Class I	RHD, MR		Alpha streptococcus; 0.05	30 days	28.8	16 weeks	None
5 320703	F 31	11-6-46	Class I	117	Class I	RHD, MR, MS		Alpha streptococcus; 0.07	44 days	19	12 weeks	None
6 321010	M 53	7-5-47	Class III	7	Dead	RHD, MR, MS	Congestive heart failure	Unknown; autopsy proof	211 days	500	40 weeks	None
7 329299	M 32	7-26-47	Class II	6	Dead	RHD, MR, AR	Congestive heart failure	Unknown; autopsy proof	30 days	300	44 weeks	Slight
8 329386	M 43	8-20-47	Class I	106	Class III	RHD, MR, MS (AR during therapy)		Alpha streptococcus; 0.078	60 days	236.2	12 weeks	None
9 342613	F 13	7-29-48	Class I	91	Class I	RHD, MR, MS		Alpha streptococcus; 0.19	30 days	120	1 week	None
10 347079	F 39	11-2-48	Class I	91	Class II	RHD, MR, AR		Enterococcus; 10.0	43 days	415	12 weeks	None
11 345984	F 32	11-9-48	Class I	91	Class II	RHD, MR, MS, AR		Alpha streptococcus; 0.039	48 days	750	36 weeks	Slight
12 352792	M 26	4-11-49	Class I	72	Dead	RHD, MR, MS, AR	Congestive heart failure	Alpha streptococcus; not done	30 days	300	16 weeks	Moderate
13 360767	M 42	11-14-49	Class I	26	Dead	RHD, MR, AR	"Coronary heart disease"	Alpha streptococcus; 0.15	30 days	288	8 weeks	Moderate
14 361817	F 33	12-23-49	Class I	81	Class II	RHD, MR, MS		Alpha streptococcus; 0.078	30 days	288	44 weeks	Slight
15 358464	F 37	4-24-50	Class III	10	Dead	Tetralogy of Fallot	Postoperative shock	Alpha streptococcus; 0.08	30 days	288	4 weeks	Moderate
16 367736	F 15	5-29-50	Class I	75	Class II	RHD, MR, MS		Alpha streptococcus; 0.01	30 days	288	4 weeks	Moderate
17 370818	F 35	8-25-50	Class I	72	Class II	RHD, MR		Alpha streptococcus; 0.03	30 days	287.7	20 weeks	Moderate

* American Heart Association.
† Sensitivity expressed as minimal inhibitory concentration in units per cubic centimeter.
‡ RHD, rheumatic heart disease; MR, mitral regurgitation; MS, mitral stenosis; AR, aortic regurgitation.

months, respectively, after cessation of therapy. The remaining patient's disease was due to an enterococcus, which required 10 units of penicillin per milliliter for inhibition. This patient (case 10) recovered following 43 days of penicillin therapy, during five days of which streptomycin was also administered.

The duration of penicillin therapy was 30 days in nine cases, from 31 to 61 days in six, and 97 days and 211 days, respectively, in the remaining two. The total dosage of penicillin administered to each patient varied from 11.7 million units given during a period of 31 days, to 750 million units of penicillin given during a period of 48 days. Case 6 as well as case 10 received streptomycin in addition to penicillin. The remaining patients received penicillin alone, with or without such agents as para-aminobenzoic acid or carinamide. The duration of symptoms of bacterial endocarditis prior to the onset of final definitive therapy in each patient is shown in table 1, and ranged from one week to two years. Cases 5, 6, 7, 10, 11, 12, 14 and 17 had received antibiotic therapy elsewhere prior to admission.

Patients were followed by study of their hospital records, by letter and telephone contact with the patients or their private physicians, or both, and in one instance by a report of the death certificate alone. Necropsy was performed on three patients.

Seven patients died from six months to six years following cessation of antibiotic therapy for bacterial endocarditis. Four died of congestive heart failure, one of "coronary heart disease," one of pulmonary tuberculosis which was diagnosed after hospitalization for treatment of bacterial endocarditis, and one of postoperative shock several hours after thoracotomy for attempted repair of a congenital malformation of the heart. Thus five patients died of heart disease and two of noncardiac causes.

Case 1 was in congestive failure at the time of discharge, and her clinical status worsened progressively in spite of low salt diet, digitalis, and restriction of activity. Congestive failure became much more severe two weeks after discharge, with the onset of abdominal swelling, increased dyspnea and leg edema. On admission to another hospital five months later she was found to have severe congestive failure, with marked aortic regurgitation and a blood pressure of 170 mm. Hg systolic and 0–30 mm. Hg diastolic. There was marked left ventricular hypertrophy. She failed to respond to vigorous therapy and died at the age of 52.

Case 3 was transferred to another institution for treatment of pulmonary tuberculosis 10 months following recovery from bacterial endocarditis. At that time she had no limitation of activity from her rheumatic heart disease, and suffered no cardiac disability subsequently. She succumbed to pulmonary tuberculosis shortly afterward.

Case 6 died seven months after cessation of penicillin therapy. He had moderate liver enlargement and moderate restriction of activity due to heart disease at the time penicillin therapy was discontinued. He was readmitted to the hospital 10 weeks later with congestive heart failure. He improved

temporarily after two weeks, but died of congestive heart failure during his third hospitalization. Necropsy revealed healed bacterial endocarditis of the mitral valve, with cardiac hypertrophy (840 gm.), old rheumatic mitral valvulitis, pulmonary infarction, multiple pulmonary arterial thromboses, and chronic passive congestion of the viscera. The aortic, tricuspid and pulmonic valves were not remarkable.

Case 7 was disabled with dyspnea at the time of discharge, and was readmitted to the hospital on three subsequent occasions during the ensuing five months. He had severe aortic regurgitation, with progressive enlargement of the left ventricle and the development of atrial fibrillation. At the time of his first admission for bacterial endocarditis the electrocardiogram was within normal limits. Necropsy showed healed bacterial endocarditis with perforation of two aortic valve leaflets, old infarcts of the kidneys and spleen, and marked chronic passive congestion.

Case 12 was discharged after an uneventful course of penicillin therapy. He was digitalized while in the hospital. There was marked aortic regurgitation, with a blood pressure of 165/0 mm. Hg. The electrocardiogram during hospitalization showed a prolonged P-R interval, with periods of 2:1 A-V block and left ventricular hypertrophy. He got along fairly well for about four years after recovery from bacterial endocarditis, but then developed increasing congestive failure and atrial fibrillation. He died rather suddenly at home two years later. Necropsy was not performed.

Case 13 was discharged with evidence of mitral and aortic valvular disease. He was followed for a year and a half in the clinic and did well symptomatically, although there was evidence of pericarditis shortly after discharge. The electrocardiogram showed signs of left ventricular hypertrophy. He died at home 26 months after penicillin therapy and seven months after having been seen in the clinic. According to the death report, his death was due to "coronary heart disease," although the details are unknown.

Case 15 died of postoperative shock several hours after thoracotomy. She had done well for 10 months following recovery from bacterial endocarditis. Necropsy revealed the tetralogy of Fallot, with right aortic arch, pulmonary arterial sclerosis, and healed endocarditis of the aortic valve.

The 10 living patients have been followed for from six to 10 years, as noted in table 1. Four are in Class I (American Heart Association Classification) as to their functional capacity, five are in Class II, and the remaining patient is in Class III. Case 2, who has been followed for 10 years, has had two children and now has no cardiac symptoms whatever. Case 16 received penicillin and streptomycin for 30 days in December, 1952, at another hospital because of congestive heart failure. Blood cultures were negative prior to this therapy. The mean ages at the time of treatment for the 10 survivors and for the five patients who died of heart disease were 31.5 and 40.8 years, respectively.

Four of the five patients who subsequently died of heart disease were

noted to have aortic regurgitation at the time of discharge following treatment for bacterial endocarditis. Three of these patients had cardiac enlargement by x-ray and clinical examination. In contrast, only three of the 10 presently surviving patients were noted to have aortic regurgitation at the time of treatment for bacterial endocarditis, and only one of these three showed cardiac enlargement.

The detrimental effect of aortic regurgitation on the prognosis is also shown by dividing the 16 patients with rheumatic heart disease into seven with aortic regurgitation and nine with mitral valve disease alone. Of the seven patients with aortic regurgitation, four are now dead and the other three have shown a decrease in functional capacity. Only one (case 8) of these seven patients developed aortic regurgitation during hospitalization for penicillin therapy, the remaining six having shown it prior to treatment. Of nine patients with mitral valve disease only, two are now dead (one of tuberculosis), three have worsened symptomatically, and four are unchanged as to their physical activity. The mean age of the seven patients with aortic regurgitation at the time of treatment was 37.8 years, and three of these were over 40 years of age. The mean age of the nine patients with mitral valve disease alone at the time of treatment was 31.1 years, two of these having been over 40 years of age.

It is noted that, from a cardiac standpoint, six of the 10 surviving patients showed evidence of symptomatic deterioration. Three of these six were noted to have aortic regurgitation at the time of hospitalization, whereas none of the four survivors who are symptomatically unchanged had such a valve lesion.

At the time of treatment for bacterial endocarditis, eight of the patients showed no evidence of cardiac enlargement, four had slight enlargement, and five showed moderate cardiomegaly on chest roentgenograms. Three of the last group have died, as have one who had slight cardiomegaly initially and three with no cardiac enlargement at the time of treatment. Of the five patients dying of heart disease, the heart size was known at the time of death in four and was markedly increased in all.

When first seen with active bacterial endocarditis, none of the 17 patients displayed atrial fibrillation, although it was noted at varying intervals following recovery in cases 7, 12, 16 and 17.

Discussion

This study confirms the reports of Katz, Brams and their associates [2, 3] on the unfavorable influence of aortic valve lesions on the subsequent course of patients with healed bacterial endocarditis. They recently reported on 17 patients followed from six and one-half to 10 years. According to their addendum report, seven of their patients had died. Six of these died of heart disease. Of these six patients, five had aortic regurgitation, whereas only three of their 10 survivors had aortic regurgitation. These findings are in striking agreement with our results. Of their 10 survivors,

seven were asymptomatic (Class I), one was in Class II, and two were in Class IV.

Segal, Harvey and Hufnagel [4] recently published a study of 83 patients with free rheumatic aortic regurgitation. A low diastolic pressure and peripheral signs of aortic regurgitation were present in all. The average patient had had symptoms for 6.4 years. However, 16 patients had been symptomatic for more than 10 years. Bacterial endocarditis had occurred previously in 18 patients (22%), an average of 3.6 years before evaluation. In five patients the murmur of aortic regurgitation was first observed after the infection, and in five others the preëxisting aortic regurgitation was aggravated. The bacterial infection was frequently followed by a progressively downhill course, suggesting consideration of the insertion of a Hufnagel valve in selected patients in this category.

Priest and Smith [5] reported the subsequent course of 21 patients who had survived for four years following cure of bacterial endocarditis. Five of their patients died, one in the fourth year, one in the seventh year, and three in the eighth year after recovery from bacterial endocarditis. Of their 16 survivors, 11 were in Class I, two were in Class II, and three were in Class III or IV.

Pillsbury and Fiese [6] observed the subsequent course of 26 patients who were apparently cured of bacterial endocarditis. Six patients died from nine months to four years, respectively, after penicillin therapy. The remaining patients had lived for from one and one-half to four years. Survival curves for four series of patients who were cured of bacterial endocarditis are shown in figure 1.

Donzelot and associates [7] followed 202 patients who were treated for bacterial endocarditis. Positive blood cultures were obtained in only two thirds of their cases. There were 49 early deaths (in the first three months after therapy) and 21 later deaths. Seventeen of the later deaths were due to congestive heart failure. The 132 survivors were followed for from four to seven years, and 120 of them were essentially asymptomatic.

Henriksen and Neukirch [8] followed 13 patients with healed bacterial endocarditis for from two and one-half to 7.3 years. Three were dead, six were disabled to varying degrees, and four were asymptomatic (table 2).

Our data, in agreement with those of others, show that some patients with healed bacterial endocarditis, particularly if they do not have aortic valve disease, may survive for as long as 10 years with no symptoms referable to their hearts. A similar viewpoint prevailed in a recent symposium in which 10 experts expressed their opinions regarding the prognosis of apparently healed bacterial endocarditis.[9]

Occasionally, unusual late sequelae of healed bacterial endocarditis have proved fatal. Priest and Smith [5] described one patient who died in the seventh year of acute myocardial infarction secondary to occlusion of a coronary artery by a piece of calcium dislodged from a healed mitral vegetation. A recently published Cabot case [10] described a mycotic aneurysm

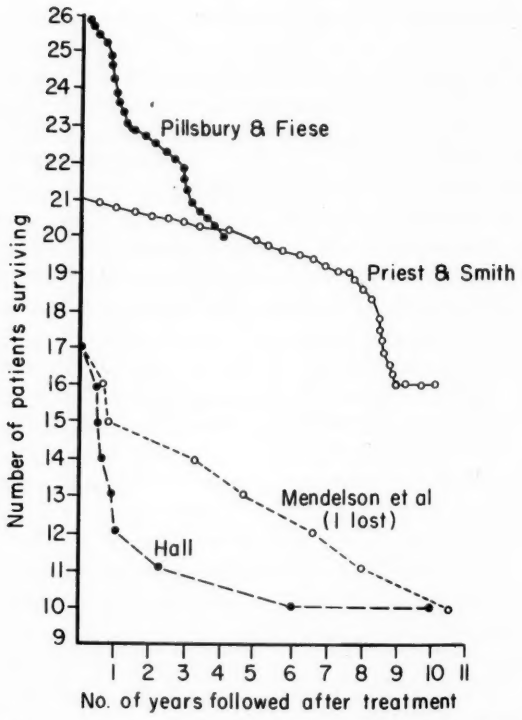


FIG. 1. Survival curves for healed bacterial endocarditis, published series. In three series, follow-up was as long as 10 years.

with perforation of the aortic leaflet of the mitral valve in a patient cured of bacterial endocarditis 10 years before. This aneurysm apparently resulted in increased stenosis and regurgitation at the mitral orifice, and doubtless contributed to the patient's progressively downhill course from congestive failure. A report [11] from the Mayo Clinic recently called attention to the fact that unrecognized healed bacterial endocarditis must be con-

TABLE 2

Tabular Summary of Reported Long-Term Prognosis in Healed Bacterial Endocarditis

	No. of Patients Cured of SBE	Duration of Follow-Up in Years	No. of Patients Dead	No. of Patients Asymptomatic	No. of Patients with Physical Limitation
Pillsbury and Fiese[6]	26	1.5–4	6	16	4
Donzelot et al.[7]	153	1–7	21	120	12
Priest and Smith[5]	21	Approx. 10	5	11	5
Mendelson et al.[3]	17	6.5–10.4	7	7	3
Henriksen and Neukirch[8]	13	2.5–7.3	3	4	6
Hall	17	6–10	7	4	6

sidered as a possible etiologic factor in every case of mitral insufficiency. Eight such cases were noted at necropsy in a period of three years. These cases presumably had been cured of bacterial endocarditis by antimicrobial agents previously given without the correct diagnosis.

Relapse of infection is uncommon nowadays and is usually discovered before the patient is discharged from the hospital. Reinfection probably occurs no more often than in a previously uninfected cardiac patient. Donzelot et al.[7] stated that a recurrence rate of 2.4% might be anticipated. There have been no proved examples of recurrence of bacterial endocarditis in our patients. Pillsbury and Fiese [6] noted one and possibly two examples of recurrence in their patients, and Mendelson et al.[3] noted one.

Summary

The present status of 17 patients who were discharged from the hospital cured of bacterial endocarditis six or more years ago was determined. During the first year after penicillin therapy five patients died, three of congestive heart failure and two of noncardiac causes. Two additional patients died 26 months and six years after penicillin therapy, of coronary heart disease and congestive failure, respectively.

Of 10 living patients followed for from six to 10 years, four are asymptomatic, five have slight limitation of activity, and one is moderately disabled.

Four of the seven patients with aortic regurgitation are now dead, and the other three have shown a decrease in functional capacity. This finding contrasts with that for nine patients who had only mitral valve disease, of whom two are dead, three have worsened symptomatically, and four are unchanged. One patient had the tetralogy of Fallot.

This study shows that some patients may remain well for from six to 10 years after recovery from bacterial endocarditis, especially if aortic regurgitation is not present.

Healed bacterial endocarditis must now be considered in the differential diagnosis of mitral regurgitation and of aortic regurgitation.

Summario in Interlingua

In le curso del septenne periodo ab 1944 a 1950, 32 patientes con endocarditis bacterial esseva admittite al Hospitales de Recerca e Instruction del Universitate Illinois. Le diagnose esseva establite in omne caso per positive culturas de sanguine in le presentia del usual tableau clinic o per necropsia. Dece-cinque del patientes moriva durante le hospitalisation initial ab non domabile grados de infection, ab congestive insufficientia cardiac, o ab altere complicationes del morbo.

Dece-septe patientes esseva dimittite ab le hospital post que un cura bacteriologic habeva essite effectuate. Le patientes supervivente esseva tenite sub observation consecutori durante un minimo de sex annos e un maximo de dece.

Omne le 17 patientes recipeva penicillina durante 30 dies o plus. Casos 6 e 10 (vide tabula 1) recipeva etiam streptomycina. Octo patientes habeva essite tractate con antibioticos ante lor admission al hospital.

Septe patientes moriva intra sex menses a sex annos post le termination del therapia antibiotic. Quatro moriva ab congestive disfallimento cardiac, un ab "morbo cardiac coronari" (secundo le certificato de defunction), un ab tuberculose pulmonar, e un ab choc postoperatori in le tentativa de reparar le tetralogia de Fallot. Cinque patientes moriva le prime anno, un post 26 menses, e un post sex annos.

Inter le patientes qui vive ancora, quatro es asymptomatic, cinque es in Classe II (secundo le classification del Association Cardiologic American), e un es in Classe III. Un patiente ha essite libere de symptomas pro 10 annos, e durante iste intervallo illa ha experientiate duo parturitiones sin incidente.

Esseva notate que quatro del cinque patientes moriente ab morbo cardiac habeva regurgitation aortic al tempore de lor dimission post le tractamento pro endocarditis bacterial, e tres de illes habeva allargamento cardiac. Per contrasto con isto, regurgitation aortic esseva notate in solmente tres del 10 patientes qui vive ancora al tempore presente, e solmente un de iste tres habeva allargamento cardiac durante le curso del therapia a penicillina. Le effecto detrimentose que le regurgitation aortic exerce super le prognose es corroborate per un comparation detaliate con le resultatos obtenite in patientes con morbo mitral.

Le datos colligite in iste e previemente publicate studios post-hospitalari de patientes con resanate endocarditis bacterial es presentate in le forma de tabulas in le texto. In nostre patientes nulle recurrentia de infection esseva observate.

Il existe in le litteratura reportos que indica que resanate endocarditis bacterial, incluse casos non recognoscite e tractate sub diagnoses erronee, deveni de plus in plus importante como factor causative o exacerbante in le genese de numerose exemplos de regurgitation aortic e de regurgitation mitral.

Le presente studio monstra que plus que un medietate del patientes qui quita le hospital con resanate endocarditis bacterial se trova vivente sex a dece annos plus tarde e que al minus un quarto de illes remane libere de symptomas cardiac. Regurgitation aortic exerce un influentia adverse super le prognose.

BIBLIOGRAPHY

1. Hall, B.: The management of bacterial endocarditis. With notes on 65 treated cases, M. Clin. North America **41**: 185, 1957.
2. Kaplan, S. R., Rosenman, R. H., Katz, L. N., and Brams, W. A.: Healed subacute bacterial endocarditis, a new entity, J. A. M. A. **141**: 114, 1949.
3. Mendelson, C. E., Cahué, A., Katz, L. N., and Brams, W. A.: Long-term outlook for healed subacute bacterial endocarditis, J. A. M. A. **160**: 437, 1956.
4. Segal, J., Harvey, W. P., and Hufnagel, C.: A clinical study of one hundred cases of severe aortic insufficiency, Am. J. Med. **21**: 200, 1956.
5. Priest, W. S., and Smith, J. M.: The effect of healed subacute bacterial endocarditis on cardiac dynamics, Arch. Int. Med. **95**: 646, 1955.
6. Pillsbury, P. L., and Fiese, M. J.: Subacute bacterial endocarditis. Follow up study of thirty patients treated with penicillin, Arch. Int. Med. **85**: 675, 1950.
7. Donzelot, E., LeBojec, J. M., Kaufmann, H., and Escalle, J. E.: Le pronostic de l'endocardite infectieuse subaiguë traitée par les antibiotiques: résultats du traitement de 202 cas, Arch. d. mal. du cœur **46**: 97, 1953.
8. Henriksen, E., and Neukirch, F.: The treatment of subacute bacterial endocarditis, Danish M. Bull. **2**: 208, 1955.
9. Medical forum on prognosis in cured bacterial endocarditis, Mod. Med. **23**: 139, 1955.
10. Castleman, B., and Bland, E. F.: Clinicopathological conference, Case 42271, New England J. Med. **255**: 39, 1956.
11. Hepper, N. G. G., Burchell, H. B., and Edwards, J. E.: Mitral insufficiency in healed unrecognized bacterial endocarditis, Proc. Staff Meet., Mayo Clin. **31**: 659, 1956.

THE TREATMENT OF ACUTE PORPHYRIA WITH CHELATING AGENTS: A REPORT OF 21 CASES *

By HENRY A. PETERS, M.D., SHERWYN WOODS,† PETER L. EICHMAN, M.D., and HANS H. REESE, M.D., F.A.C.P., *Madison, Wisconsin*

ACUTE porphyria, especially its therapy, has challenged the clinician for years. The mortality rate when associated with severe neuropsychiatric manifestations is quoted as from 80 to 90%.[1] Favorable therapeutic response to 2,3-dimercaptopropanol (BAL)‡ and disodium calcium ethylene diamine tetra-acetate (EDTA)§ was reported by Peters [2, 3] in seven of 10 cases of acute porphyria, and by McCabe [4] in one case of acute porphyria benefited by BAL administration. Paul and Thyresson [5] and Schrumpf [6] reported the ameliorating effects of BAL in cutaneous porphyria. Dean [7] recorded one case not benefited by BAL.

A total of 30 porphyria cases, including our previously reported patients,[2, 3] have been studied. BAL and EDTA therapy in 21 of these patients forms the basis of this report on the efficacy of chelation treatment in this metabolic disorder. ‖

CASE MATERIAL

Watson [8] has divided porphyria into two major forms: the porphyria erythropoietica, in which the metabolic error resides in the bone marrow, with onset in infancy of mutilating photosensitive dermatitis; and hepatic porphyria, which he subdivides into acute, cutanea tarda, mixed and latent forms.

Acute hepatic porphyria, inherited as a mendelian dominant, is characterized by recurrent gastrointestinal, psychiatric and neurologic symptomatology, occurring singly or in combination. Whereas erythropoietic porphyria is rare, we are of the opinion that hepatic porphyria is much more common than is suspected.

Hepatic cutanea tarda porphyria is manifested by the late onset of photosensitive cutaneous lesions.

* Presented at the Thirty-eighth Annual Session of The American College of Physicians, Boston, Massachusetts, April 11, 1957.

From the Department of Neurology, University of Wisconsin Medical School, Madison, Wisconsin.

† Senior student in medicine, University of Wisconsin.

‡ Referred to henceforth as BAL.

§ Referred to henceforth as EDTA.

‖ Disodium calcium versenate was supplied by the Riker Laboratories and bisodium versenate by Abbott Laboratories.

Requests for reprints should be addressed to H. A. Peters, M.D., Neurology Department, University Hospitals, Madison, Wisconsin.

Hepatic mixed porphyria refers to a combination of the cutaneous and acute varieties. It is important to recognize that both latent and asymptomatic forms of the disease exist.

Based on Watson's classification, our studies include 26 acute intermittent cases, one mixed hépatic porphyria and three latent types. Twenty of the acute intermittent cases and the one mixed porphyria were treated. No latent cases have been subjected to therapeutic efforts. Sex ratio was 2:1 in favor of the women. Age ranged from 22 to 55 years.

Methods of Treatment and Agents Used

BAL was used in a 10% solution in 20% benzyl benzoate in peanut oil. Doses ranged from 50 to 1,200 mg. per 24 hours in divided doses. Therapy varied from four to 60 days consecutively. In several cases one to three injections of 100 to 300 mg. weekly for as long as two years have been employed. With the exception of a questionably related transient erythema multiforme, no toxic effects of BAL or EDTA have been encountered. In 11 cases BAL was the only agent used. In six patients BAL was combined with intravenous EDTA in either acute or chronic phases of the disorder. EDTA intravenous dosage varied from 1 to 10 gm. in a 24-hour period, diluted in 5% glucose in water in a ratio of 2.5 to 5 gm. of EDTA per 1,000 c.c. The medication was administered over two to four hours, and two to five consecutive days constitute the usual course of treatment. Fourteen days of total treatment were reached in one case. Oral EDTA in 0.5 gm. tablets was occasionally used in subacute phases, the daily dose varying from one to three tablets. Four patients were in extremis after ACTH therapy; when chelation was initiated they showed prompt improvement. In three other patients, however, ACTH proved beneficial after equivocal or poor response to chelation therapy. Two patients (case 1)[3] received hydrocortisone for several days during chelation because of oliguria, and diuresis promptly followed. The choice of chelating agent depended in part on a history of lead exposure, EDTA then being used preferentially. Urinary lead excretion levels were borderline in several cases, and lead diuresis was noted during chelation.

After the diagnosis has been made or suspected, barbiturates, sulfonamides, alcohol, heavy metals, exposure to oil paints, solvents and sunbathing must be studiously avoided. Thorazine, Demerol, Paraldehyde, Frenquel and intravenous procaine were used very occasionally, and they were infrequently needed during chelation or thereafter. One patient with neurologic and psychiatric symptoms seemed exceptionally sensitive to Thorazine, responding with ataxia, nystagmus, aphasia and general clinical deterioration.

In addition to our chelation regimen, exceptional nursing care, tracheotomy and careful attention to fluid and electrolyte balance must be credited in bringing about clinical recovery.

Laboratory Findings

In our laboratory the following are accepted as upper normal values in the urine: porphobilinogen, 1.0 mg./L.; delta-amino levulinic acid, 2.5 mg./L.; zinc, 0.5 mg./L.; lead, 0.05 mg./L. Uroporphyrin and coproporphyrin were graded 0 to 5 plus.

All patients had porphobilinogenuria, and all cases except two excreted uroporphyrins. Eight of nine patients had zinc values of from 1.0 to 18.9 mg. before chelation therapy. Whereas the acuteness and severity of the clinical cases correlated with excessive excretion of zinc, excretion of abnormal porphyrin metabolites including uroporphyrin did not parallel symptoms.

In some cases elevation of from two to eight times normal urinary zinc excretion was observed, and corresponded to severe clinical symptoms (i.e., convulsions, schizophrenic-like excitement and tremors), despite apparent normality of urinary porphyrin excretion and very occasional porphobilinogenuria.

Clinical Symptomatology

A variety of clinical syndromes has been described.[1, 3, 8-12] In the symptomatic patients of our series, multiple signs and symptoms were encountered.

Central Nervous System: Eight manifested bulbar symptoms in the form of dysphagia, diplopia, anisocoria, and facial and/or laryngeal palsies. Three patients had Jacksonian seizures and seven the grand mal type. Homonymous hemianopsia and contralateral seizure activity, alternating from one side to the other and accompanied by focal electroencephalographic spiking, were seen in one patient. Aphasia and apraxia were demonstrated in two cases. Thirteen patients had such psychiatric symptoms as excited catatonic, schizophrenic-like psychosis, and hysterical and depressive reactions; the level of consciousness ranged from torpor to coma.

Peripheral Nervous System: Eight cases presented peripheral neuropathy. In one patient a painful dysesthetic, trigeminal neuralgia was seen. Patients with severe peripheral neuropathy have shown complete recovery, except for case 1, who is rapidly approaching normal. Periarteritis was diagnosed by muscle biopsy in one porphyric who died despite steroid and last minute chelation therapy.

Paresis caused by porphyria is as often distal in onset as proximal. It may be accompanied by myoclonic movements, asynchronous muscular contraction (especially against resistance), and generalized involuntary motor excitation upon volitional motion of a single extremity. Despite complete tetraplegia, such heightened motor irritability was seen in three patients.

Sensory complaints may be severe in the absence of objective sensory deficits. Descriptions of pain have been vague and poorly localized, perhaps reflecting the altered level of consciousness. Distinction from hysterical syn-

dromes may be difficult. Abdominal, back or chest pain was frequent, and those with back pain often assumed the knee-chest position. Multiple laparotomies (15 in one case) and laminectomy were recorded. Habituation to opiates or Demerol was not unusual.

Gastrointestinal Tract: Obstipation was noted in 12 patients. Diarrhea was seen in two cases, one of whom had frequent bloody stools (case 1).

Genitourinary: Two patients had temporary oliguria and another urinary retention. Recurrent suprapubic pain was seen in one. *The Burgundy wine or brownish urine commonly described in textbooks was seldom mentioned by the patient.* Often the urine was of normal color, which occasionally changed to brown, red or black after exposure to sunlight. Urinary odor was often offensive.

Skin: A malar flush, diffuse dusky complexion and hirsutism were noted. Cutaneous bullae were seen in our one case of hepatic mixed porphyria. Intolerance to sunlight, oil-based paints, chemical solvents, barbiturates and lead was commonly observed. In several cases dietary substances such as peas, corn and tomatoes seemed related to exacerbations of the disease. One case developed a severe cerebellar ataxia and psychosis after administration of Thorazine. Periorbital and parotid swelling during exacerbations was noted in one case.

Case Reports

Case 1. The patient, age 30, was admitted to University Hospitals on May 8, 1956. Four years earlier the patient had had transient melena, ascribed to hemorrhoids. As a child he had had episodes of colitis lasting several weeks at a time. Malarial attacks had been present during adolescence, but health had otherwise been good. Five weeks before admission he developed abdominal pain and diarrhea which became bloody. Surgery was performed, using intravenous Pentothal anesthesia, at his local hospital, but no Meckel's diverticulum or other pathology was found; a normal appendix was removed. Following surgery the patient developed muscle cramps, difficulty in breathing, and a psychosis resembling catatonic excitement. After several days he was unable to lift his arms or turn himself in bed. Urinary porphobilinogen was positive, and he was treated with 40 units of ACTH gel daily, beginning on May 5, 1956, as well as calcium gluconate, Demerol and Frenquel. Spinal fluid showed 1 cell, sugar of 120 mg.% and protein of 18 mg.%.

Because of severe peripheral neuropathy and persistent psychosis, the patient was transferred to University Hospitals, where the diagnosis of porphyria was confirmed. On admission the blood pressure was 140/110 mm. of Hg; pulse, 150; respirations, 28/min. The patient was extremely agitated and hallucinating. Congenital colobomas were present. A sacral decubitus ulcer was present. Basilar râles were present in both lungs. The patient was unable to move arms or legs spontaneously, and constant myoclonic-like jerks were present throughout the muscles of the extremities, face and trunk. Severe atrophy was present in most muscle groups; positive deep tendon reflexes were present only in the Achilles and left knee jerk. The patient was dehydrated and appeared toxic. His voice was hoarse, due to paralysis of right recurrent laryngeal nerve. Tracheotomy was performed, since the patient was unable to close his glottis sufficiently to cough up secretions. Copious bloody diarrheal stools were frequent. Urinary zinc excretion was 18.5 mg./1,000 c.c., or 36 times normal, and urinary lead excretion was 0.08 mg./L. Urine copro-

porphyrin was 5 plus, uroporphyrin was positive, and there were quantitative porphobilinogen levels of 120 mg./L. on the day of admission. Hemoglobin was 15.2 gm. %, and white blood cell count 14,000 per cu. mm. with 75% polynuclear cells. Following initial studies, the patient was given chelation therapy with EDTA, 3 gm. in 2,000 c.c. 5% glucose. Energetic nursing care, with frequent suctioning of secretions, oxygen and correction of electrolyte imbalance were necessary. The psychosis and the patient's general condition improved almost immediately. With chelation, urine excretion of zinc and lead assumed levels as high as 54 mg. zinc/L. of urine.

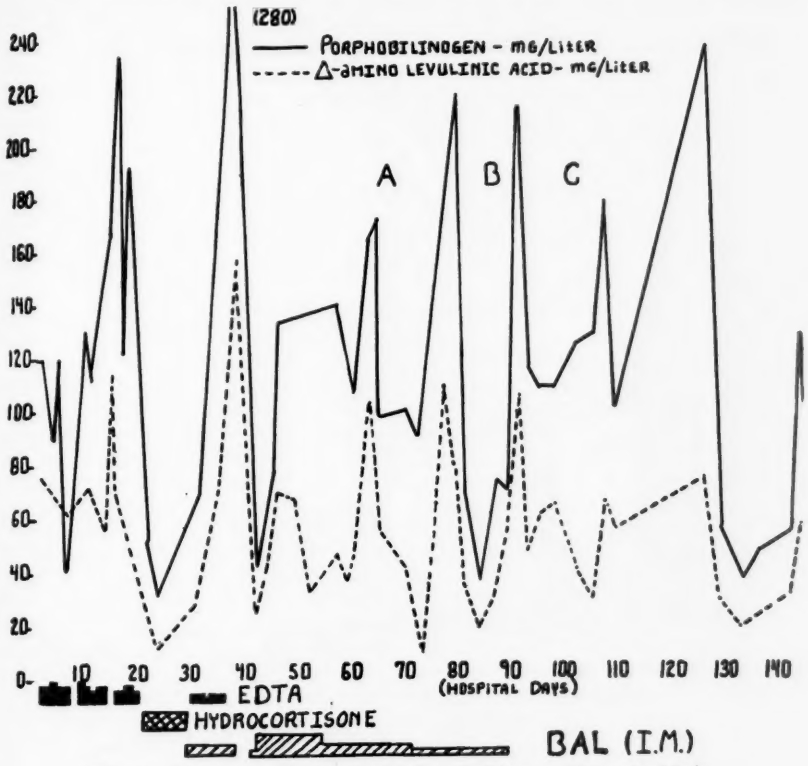


FIG. 1. *Case 1.* A. Up in wheelchair. B. Moves self in wheelchair. C. Laryngeal paralysis ends; patient walking.

On June 6, 1956, the thirtieth hospital day, urinary volume fell and peripheral edema of the extremities appeared. At this time hydrocortisone was administered over an eight-day period, with very favorable influence on the edema and renal status. Thereafter the patient was given BAL, 2 c.c./day, supplemented by oral EDTA, 2 gm. daily. Of major concern was the persistence of bloody diarrheal stools, 12 to 14 daily, playing havoc with electrolyte and water balance. BAL therapy was continued through August 4, 1956, the eighty-ninth hospital day, having been tapered to 1 c.c. daily as of July 15, 1956, the sixty-ninth hospital day. Urine zinc excretion had reached normal levels, whereas porphobilinogen and quantitative delta-amino levulinic acid levels continued to be elevated (figures 1 and 2). Muscle

strength gradually returned, diarrhea ended, phonation and glottic function had returned by August 16, 1956, the one hundred first hospital day, and the patient was discharged on November 17, 1956, the one hundred ninety-third hospital day, at which time he walked and fed himself with assistance.

In January, 1957, he was seen in the out-patient department. He was able to walk a block, could feed himself, and showed evidence of continued improvement in muscle function. There had been no return of diarrheal symptoms.

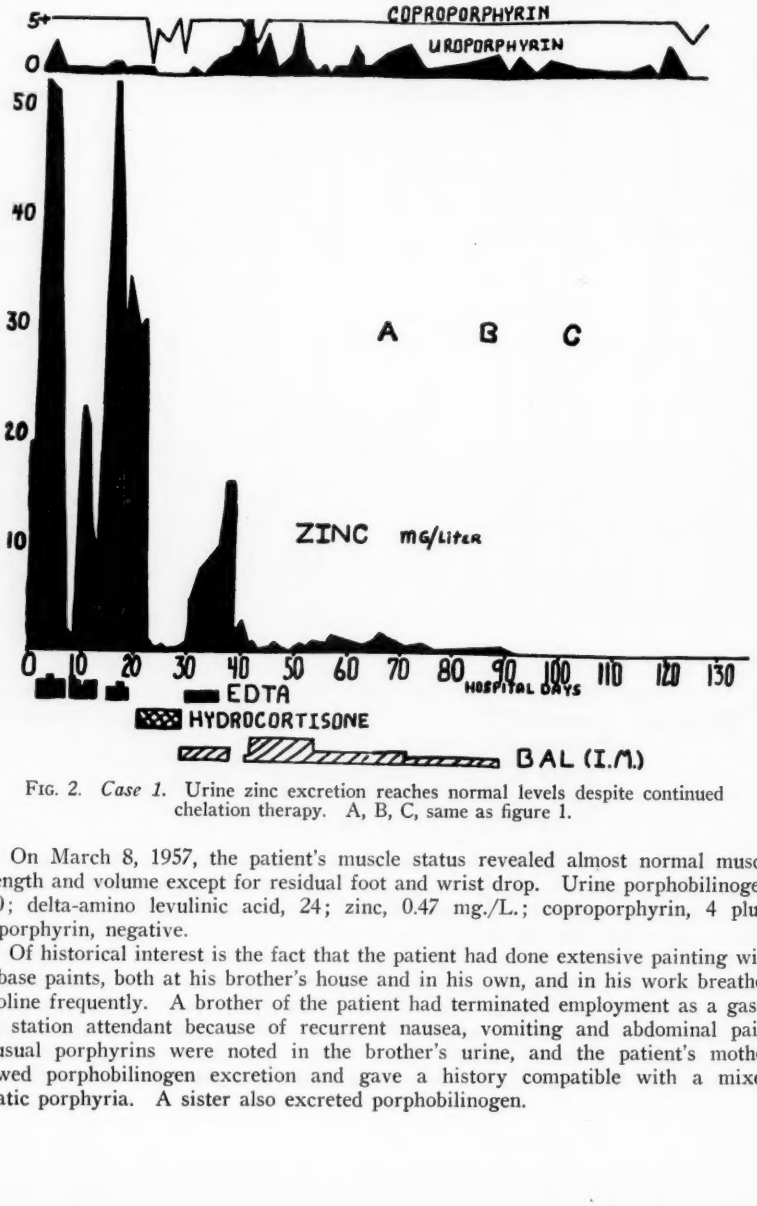


FIG. 2. *Case 1.* Urine zinc excretion reaches normal levels despite continued chelation therapy. A, B, C, same as figure 1.

On March 8, 1957, the patient's muscle status revealed almost normal muscle strength and volume except for residual foot and wrist drop. Urine porphobilinogen, 58.0; delta-amino levulinic acid, 24; zinc, 0.47 mg./L.; coproporphyrin, 4 plus; uroporphyrin, negative.

Of historical interest is the fact that the patient had done extensive painting with oil-base paints, both at his brother's house and in his own, and in his work breathed gasoline frequently. A brother of the patient had terminated employment as a gasoline station attendant because of recurrent nausea, vomiting and abdominal pain. Unusual porphyrins were noted in the brother's urine, and the patient's mother showed porphobilinogen excretion and gave a history compatible with a mixed hepatic porphyria. A sister also excreted porphobilinogen.

Complete return of muscle function is anticipated with this patient, and it should be emphasized that physical therapeutic measures were employed from the onset of his hospitalization at University Hospitals and continued after the patient's discharge.

Case 2. A 36 year old housewife was admitted to University Hospitals on May 8, 1956. Chief complaint was severe abdominal pain of two weeks' duration, of burning character and of increasing intensity three or four days prior to hospitalization. Use of Demerol had been required as often as every three to four hours to control the pain during hospitalization elsewhere. Barium enema, an upper gastrointestinal series, cholecystogram and other studies were negative. Constant nausea and emesis required intravenous feedings. Severe burning pain in the arms and legs was present. A similar attack, diagnosed as acute pancreatitis, had occurred a year before and had required hospitalization for five weeks.

Past history included episodes of diarrhea but no constipation. As a youngster the patient had developed nausea and emesis after prolonged exposure to the sun. She had had an appendectomy in 1936 and a left ovarian cystectomy in 1946. Several weeks prior to onset of symptoms the patient had been painting with enamel.

Family History: The parents had separated; the father was a "food faddist," many foods causing him to have stomach upset. Two brothers of the patient had had no illness. Married since 1946, the patient had four children, living and well. After the birth of the third child the patient experienced pain in the left leg for three weeks which required bed-rest, but she gradually improved without permanent difficulty. During the last three months of the fourth pregnancy the patient had also had severe pain in the left leg, which receded.

On admission the patient was writhing on the bed, clutching her abdomen and complaining bitterly of unrelenting pain. The knee-chest position gave her some relief. There was tenderness on palpation of the legs. Although denying hallucinosis, she recalled hearing her absent husband talking to her while en route in the ambulance. Serum lipase, 1.3; serum amylase, 114. Urinary studies for coproporphyrin and uroporphyrin were positive; and there was urinary excretion of 74 mg./L., delta-amino levulinic acid and 93 mg./L. porphobilinogen. Admission zinc urine excretion level was 1.45 mg./1,000 c.c. Despite the use of Demerol, intravenous procaine and Thorazine, the patient continued to complain bitterly. On May 10, 1956, she appeared confused. The urine excreted was dark amber. She was given 5 gm. disodium calcium EDTA intravenously, and by morning the pain was reduced and she felt better. Five grams EDTA were repeated on May 12, 1956, and 10 gm. EDTA on May 13, 1956, and May 14, 1956. Urinary coproporphyrin continued to be 5 plus, uroporphyrin 2 plus, but porphobilinogen levels and delta-amino levulinic acid were now 36 and 16, respectively. Zinc excretion reached levels as high as 11.6, and toxic urinary levels of lead were observed during chelation. Chelation was halted after May 14, 1956, because of clinical improvement. On discharge the patient was asymptomatic. Urinary zinc, 1.25 mg./L.; porphobilinogen, 20 mg./L.; delta-amino levulinic acid, 11 mg./L.

Following discharge the patient felt weak but was without pain. There was gradual return of nausea and vomiting, which promptly ceased when she began oral EDTA tablets in a dosage of 1 gm. for 10 days, followed by a rest period. When it became apparent that abdominal pain and soreness of the muscles became worse when she was not taking EDTA, she took 1 gm. of oral EDTA daily and her clinical course stabilized. Whereas in the past there had been severe abdominal pain associated with onset of the menstrual period, she failed to experience recurrence of these symptoms while on medication. As of January, 1957, the patient had all but regained her former strength and continued to be asymptomatic on 0.5 gm. oral EDTA daily. Excretion of zinc in random urine samples varied from 0.67 mg./L. to 0.84/L. Quantitative porphobilinogen values ranged between 18 and 20 mg./L.; delta-amino levulinic acid, 12 mg./L.

It should be emphasized that the patient required no Thorazine or analgesic medication following onset of an active chelation program.

Results

Four categories of response were seen: (1) improved: prompt and progressive improvement in clinical status following initiation of chelation; (2) equivocal: unsustained response, either improvement or worsening, not definitely related temporally to the initiation of chelation; (3) no change; (4) worsening: clinical worsening or death despite chelation.

Thirteen cases of acute intermittent type were improved. The single mixed porphyria improved. Four patients responded equivocally. In two there was no change. One patient with periarteritis and porphyria died despite steroid and, later, brief BAL therapy. No substantial difference was noted in the BAL or EDTA regimens of therapy, although in dosage used, response to BAL may have been more rapid than to EDTA.

We appreciate the lack of controls, the unpredictability of spontaneous remissions and the variation of severity so characteristic of this disease. However, our results are strongly suggestive, in view of the high mortality reported in severe cases by others and the prompt improvement noted in our severely ill patients following chelation.

Discussion

The clinical impression of favorable results with chelation therapy in porphyria caused us to speculate as to a determining rationale.

Analytic investigations of porphyrin biosynthesis [8, 13, 14] indicate that succinate and glycine unite to form delta-amino levulinic acid, which condenses to form porphobilinogen. Porphobilinogen then provides pyrrol units from which different isomeric series of uroporphyrin, coproporphyrin and protoporphyrin originate. An enzymatic block at one of these levels of transformation could account for the withdrawal and excretion of important metabolites from the system. Peters [2, 8] suggested that zinc accumulation, or perhaps accumulation of another heavy metal, might be responsible for such an enzymatic block, and that chelation of these cations by BAL and/or EDTA corrects the metabolic error. Increased levels of zinc excretion in the urine before chelation are in support of this view. In case 1 the 24-hour zinc excretion was 18.9 mg./L., and lead values, 0.08 mg./L. During chelation the daily zinc excretion reached a peak level of 34.8 mg./L., falling to a normal after 42 days of treatment with BAL and EDTA (figure 2). Zinc excretion then remained normal despite continued chelation.

In those patients responding to therapy, uroporphyrinuria, high levels of porphobilinogen and delta-amino levulinic acid in the urine were observed, and little correlation between these levels and symptomatology was seen during chelation. The heightened excretion of zinc during chelation sug-

gests rapid neutralization of heavy metal toxicity by binding and removal from vulnerable enzyme systems.

The level of zinc excretion prior to chelation correlated fairly well with the severity of the disease. Since other heavy metals are influenced by chelation (i.e., lead, cobalt, magnesium, manganese, copper and iron),[15] the rôle of excess zinc ions is difficult to assess.

Zinc ions are part of the metallo-enzymes, carbonic anhydrase, uricase, catalase, peroxidase, carboxypeptidase, lactic dehydrogenase and alcohol dehydrogenase.[16, 17, 18] An excess of zinc is known to inhibit the enzymatic activity of lactic dehydrogenase [17] and gonadotropin,[16] and insulin activity is slowed by 40% on addition of zinc.[19] Nesbitt [20] suggested that zinc deficiency may play a rôle in porphyria, whereas our results with chelation support a zinc intoxication theory. Batchelor et al.[21] concluded that zinc workers absorb and excrete zinc in amounts considerably over normal, and maintain constantly a higher normal zinc content. Abnormal amounts of zinc may enter and leave the body for years without causing clinical symptoms or even subjective complaints of significant gastrointestinal, renal or other focal organic pathology. However, they quote cases of Landouzy and Maumené [22] and Sacher,[23] where zinc "poisoning" produced vomiting, intestinal colic, constipation, emaciation and sometimes muscular paralysis with atrophy. Perhaps a genetically determined metabolic error in porphyria renders these subjects more vulnerable to zinc poisoning.

Bashour [24] reported that EDTA influences pyrrol metabolism directly, perhaps unrelated to its effect on heavy metals, which is assumed to be secondary. Thus we see that an acceptable explanation for chelation effectiveness in porphyria remains uncertain. The ultimate answer may be found in an increased understanding of metallo-enzyme systems.

Conclusions

Symptomatology of 25 porphyria cases is summarized. Evidence strongly suggested the favorable effect of chelation in 14 of 21 acute porphyria patients, among whom was included one case of hepatic mixed porphyria. BAL and EDTA are both effective, although in the dosage employed BAL at times seemed to act more rapidly. Renal failure appearing in acute porphyria, with or without chelation, may be reversed by hydrocortisone and does not recur with additional BAL or EDTA therapy. Chelation may be effective after failure with ACTH, and vice versa.

Heroic nursing and supportive care, including tracheotomy, are essential in severe cases. All cases must avoid exposure to barbiturates, sulfonamide, heavy metals, oil paints and solvents. Marked Thorazine sensitivity was noted in one patient with neuropsychiatric symptoms.

Elevation of zinc urine excretion is noted during acute episodes *preceding chelation* and parallels the symptoms more closely than abnormal porphyrin excretion.

The action of chelation and a rationale for its use in acute porphyria are discussed.

ACKNOWLEDGMENT

We are indebted to Dr. F. L. Kozelka and Mrs. Wanda M. McCarty for their invaluable guidance and assistance in this study.

SUMMARIO IN INTERLINGUA

Esseva studiate 30 casos de porphyria. Vinti casos de porphyria acute e un caso de mixte porphyria hepatic esseva tractate per chelation con dimercaptopropanol (BAL) o binatrium-calcium ethylenediaminotetraacetate (EDTA). Dece-tres casos de porphyria acute e le caso de mixte porphyria hepatic beneficiava ab iste therapia. In quatro casos additional le responsa esseva equivoc; in duo nulle responsa esseva notate. Un patiente con periarteritis nodose associate con porphyria moriva in despecto de tractamento con steroides e subsequentemente con agentes de chelation.

Le symptomatologia includeva symptomas neuropsychiatric, i.e. per exemplo grand mal e convulsiones focal, tetraplegia, e psychosis schizophrenoide in certe casos durante que symptomas gastrointestinal se manifestava in alteres. Le plus sever casos respondeva per restablimento complete, ben que le tetraplegicos requireva grados maximal de servicios infirmari e mesuras supportative como per exemplo tracheotomia.

Barbituratos, sulfonamidos, metallos pesante, e exposition a colorantes a oleo como etiam a dissolventes debe esser evitate.

Elevation del excretion urinari de zinc esseva observate in iste patientes ante le uso del agentes de chelation. Illo esseva plus clarmente parallel al severitate del symptomas que le excretion anormal de porphyrina. Es supponite que le elimination de zinc e altere metallos pesante per le chelation resulta in un interruption del bloco metabolic que es inducite per ille cationes in casos characterisate per le error metabolic de porphyria acute.

ACTH non succedeva a arrestar le curso descendente de tres patientes con tetraplegia, sed chelation effectuava un reversion del resultato que habeva parite terminal. ACTH esseva usate in un altere patiente qui non respondeva al programma de chelation. Hydrocortisona reverteva sever formas de oliguria in duo patientes. Duo casos es reportate in detalio.

BIBLIOGRAPHY

1. Markovitz, M.: Acute intermittent porphyria: a report of five cases and a review of the literature, Ann. Int. Med. **41**: 1170, 1954.
2. Peters, H. A.: BAL therapy of acute porphyrinuria, Neurology **4**: 477, 1954.
3. Peters, H. A.: Therapy of acute porphyria with BAL and other agents, Dis. Nerv. System **17**: 177–183, 1956.
4. McCabe, E. S.: Case report: recovery in a case of ascending Landry paralysis due to porphyria, Am. Pract. **6**: 878, 1955.
5. Paul, K. G., and Thyresson, N.: The effect of BAL on a case of "cutaneous porphyria," Acta dermat.-venereol. **34**: 403, 1954.
6. Schrumpf, A.: Porphyria improved after treatment with BAL, Acta med. Scandinav. **145**: 338, 1953.
7. Dean, G.: Porphyria, Brit. M. J. **2**: 1291, 1953.
8. Watson, C. J.: Porphyria, *in* Advances in internal medicine, edited by W. Dock and I. Snapper, Vol. 6, 1954, Year Book Publishers, Chicago, pp. 235–299.
9. Schmid, R., Schwartz, S., and Watson, C. J.: Porphyrin content of bone marrow and liver in the various forms of porphyria, Arch. Int. Med. **93**: 167, 1954.

10. Kark, R. M.: Clinical aspects of the major porphyrinopathies, M. Clin. North America **39**: 11, 1955.
11. Rimington, C.: Haems and porphyrins in health and disease. Part II, Acta med. Scandinav. **143**: 177, 1952.
12. Vanotti, A.: Porphyrins, 1954, Hilger and Watts, London.
13. Shemin, D.: The succinate-glycine cycle; the role of delta-amino levulinic acid in porphyrin synthesis, *in* Ciba Foundation symposium on porphyrin biosynthesis and metabolism, edited by G. E. W. Wolstenholme and E. C. P. Millar, 1955, Little, Brown & Company, Boston, pp. 4–26.
14. Aldrich, R. A., Labbe, R. F., and Talman, E. L.: A review of porphyrin metabolism with special reference to childhood, Am. J. M. Sc. **230**: 675, 1955.
15. Chenoweth, M. B.: Chelation as a mechanism of pharmacological action, Pharmacol. Rev. **8**: 57, 1956.
16. Vallee, B. L.: The metabolic role of zinc, J. A. M. A. **162**: 1053, 1956.
17. Wacker, W. E., Ulmer, D. D., and Vallee, B. L.: Metalloenzymes and myocardial infarction, New England J. Med. **255**: 449, 1956.
18. Borden's Review of nutritional research **17**: No. 4, 1956.
19. Scott, D. A., and Fisher, A. M.: Effect of zinc salts on the action of insulin, J. Pharmacol. and Exper. Therap. **55**: 206, 1935.
20. Nesbitt, S.: Acute porphyria, J. A. M. A. **124**: 286, 1944.
21. Batchelor, R. P., Fehnel, J. W., Thomson, R. M., and Drinker, K. R.: A clinical and laboratory investigation of the effect of metallic zinc, of zinc oxide, and of zinc sulphide upon the health of workmen, J. Indust. Hyg. and Toxicol. **8**: 322, 1926.
22. Landouzy and Maumené: De l'intoxication zincale observée chez les ouvriers tordeurs de fils galvanisés, Gaz. méd. de Paris **5**: 409, 1850.
23. Sacher, A.: Zur Kenntnis der Wirkung der Zinksalze, Arb. des pharmakol. Inst. zu Dorpat, Stuttgart **9**: 88, 1893.
24. Bashour, F. A.: Lead poisoning with special reference to porphyrin metabolism, Bull. Minn. Hospitals & Med. Found. **26**: 423, 1955.

THE ROLE OF THE INTERNIST IN RESTORATIVE SERVICES FOR THE AGED*

By S. D. Pomrinse, M.D., *Washington, D. C.*

In this discussion I shall use the term *restorative services* rather than *rehabilitation* to identify services provided by the physician and other professional and technical personnel in allied medical fields to improve or at least to maintain the physical and functional capacity of a patient. The term *restorative services* seems more appropriate than *rehabilitation,* since the latter generally implies vocational goals, and obviously we are less likely to be concerned with them when dealing with older persons. My discussion will therefore be concerned with a dynamic medical program for restoring maximal possible function in an older patient. Primary emphasis will be on developing his capabilities to care for himself to the maximal degree.

With the continuing increase in the number of older people, and because of the internist's special competence in diagnosis and management of a wide spectrum of illness, the internist may expect to be confronted increasingly by the medical problems of an aging population. He will see, more and more, the disabling residuals of long-term illnesses that produce not only formidable health problems, but also equally significant and difficult economic and social traumata. These almost invariably accompany and complicate medical management of the older patient.

That the health problems of older people already are an ever-increasing challenge to the internist and to his colleagues in medicine is clearly evident. Estimates [1] indicate that in 1950 there were 5.3 million people in the United States who were incapacitated by illness lasting longer than three months, and which were sufficiently serious to require some form of care. In the age groups under 45, the number disabled by long-term illness constitute 1.3% of the total number. Those in the age group 45 to 64 have a disability rate of 5.8%, while in the age group 65 and older, 17.1% have long-term disability. Although precise data on disease prevalence are not now available, estimates which have been prepared [2] suggest that there are some 10 million with diabetes, 10 million with arthritis and rheumatism, 1 million with glaucoma, over 700,000 with cancer, 1.5 million with epilepsy, 500,000 with cerebral palsy, 300,000 with multiple sclerosis, 100,000 paraplegics, and 100,000 with muscular dystrophy.

Until now, medical care has served mainly to manage short-term illness

*From the Symposium on Rehabilitation, presented at the Thirty-eighth Annual Session of The American College of Physicians, Boston, Massachusetts, April 11, 1957.

From the Division of Special Health Services, Department of Health, Education, and Welfare, Washington, D. C.

Requests for reprints should be addressed to S. D. Pomrinse, M.D., Medical Director, Chief, Health of the Aged, Chronic Disease Program, Division of Special Health Services, Department of Health, Education, and Welfare, Washington 25, D. C.

and the emergency situations arising in long-term illness. Until we discover the means to cure many of the chronic diseases, physicians must employ measures which will enable patients disabled by those diseases to live as full lives as possible within the limits of their restricted capabilities.[3] In other words, we internists now are not satisfied with therapy based on symptoms alone, but we insist that etiology be considered as well. In addition, we must proceed to the consideration of therapy based on maximal restoration of function. If we consider each patient in the light of this threefold approach—symptoms, etiology and function—we will arrive at a plan of treatment which will yield maximal results. An example here is the patient with a painful joint. Symptomatic therapy alone would aim at the relief of pain. Etiologic therapy would try to determine whether this was rheumatoid arthritis, gout, lupus erythematosus or some other condition. Treatment based on function would be concerned with the degree of disability resulting from the illness and how maximal function could be restored. Obviously, no single approach is enough.

Restorative therapy will prevent deformities and loss of function and will enhance or promote the development of maximal capacity for self-care. These are realistic and necessary goals. The practicality and need for restorative services are becoming increasingly evident in the experiences reported in the rapidly growing literature dealing with rehabilitation. As a result of his experience in providing rehabilitation or restorative services for aged patients, Dacso [4] suggests that ". . . the physician of tomorrow will have to learn that he is not a mere custodian of physical health, but that mental, social and vocational problems of his patients are also his concern." There is convincing evidence that restorative medical services, started as soon as possible following the onset of illness, can help materially to minimize or prevent the development of disability residuals. Thus, Buchanan [5] has reported that almost 90% of acute hemiplegic patients can be restored to self-care within an average hospital stay of 30.7 days.

The internist, we agree, should be aware of the skills of his colleagues in the other medical specialties and in those related to medicine, such as dentistry, nursing, physical therapy, nutrition and social service, and should be capable of marshalling and coördinating the services which these specialists can offer his patients. Nevertheless, he has a fundamental responsibility for diagnosis and the planning of treatment.

In the management of hemiplegia, for example, a simple measure such as proper positioning of the patient in bed can do much to prevent the development of frozen shoulder, fibrous ankylosis of the everted dropped foot, or flexion contractures. As the acute episode subsides, the use of appropriate exercises, bracing and muscle stretching should be considered. If there are no contraindications, these measures will help to offset the predominance of flexor tone which develops and which otherwise may produce flexion deformities. The internist must, however, plan treatment cognizant of the possible danger of precipitating another cerebral or pulmonary

embolism. However, experience has shown that older patients are much less fragile than they are usually considered to be; and that they respond well to active therapy.

Arthritic patients, specifically those with osteoarthritis, comprise a significant segment of the patients in the older age group. For the arthritic patient, restorative medical services can do much to alleviate or eliminate pain. Such services can also preserve and improve the function of the affected joints, and correct the usually disturbed body mechanics resulting from the concomitant skeletomuscular inadequacy which develops almost invariably.

Long, uncut toenails, corns and callosities, hallux valgus and bunions are frequently the cause of much of the foot trouble common to older people. Relatively simple foot care measures can do much to eliminate the disability these conditions produce. One may think that this type of care is hardly "dignified" enough to be included under the heading of restorative services; however, if it permits a greater degree of functional capacity, any procedure merits such recognition.

Hip fractures are an altogether too frequent affliction of old people, as is amputation of the extremities. For such patients, restorative medicine may make the difference between a bed-bound individual and one capable of ambulation and complete self-care.

While the surgeon, the physiatrist, the physical therapist and the occupational therapist must be called upon to provide consultation and appropriate treatment, the internist nevertheless must diagnose accurately, and coördinate treatment. It is the internist who views the "whole" patient. He must recognize the existence of social and economic difficulties, and enlist the assistance of the appropriate allied professional.

He can also call into play the supporting resources of the community to cope with the varied needs of the chronically ill patient. A number of voluntary agencies operating on a nationwide scale give direct service to persons suffering with the particular chronic disease or condition with which the agency is concerned. Community welfare agencies and specialized social agencies are available for counseling and referral services. Home care programs operating out of voluntary and governmental hospitals provide many services. These may include physicians' visits, bedside nursing care, housekeeping service, physical and occupational therapy, and social casework. Visiting nurse associations and public health nursing services of local health departments provide additional resources for the care of patients with long-term illnesses that often are available to the internist. Public welfare departments can offer financial assistance to eligible patients. The health department can offer laboratory services, organizational skills, follow-up of patients, instructive nursing and health education along with its other functions.

The internist has the skills necessary to evaluate the progress the patient makes in convalescence. He must assess the priority of treatment needs,

and provide or order such measures as he considers appropriate. He will benefit his patient most when he keeps constantly in mind a *functional goal* based upon the principle of helping the patient to do "as much as he can, as well as he can, as long as he can."

It may be that, to develop this skill, some additional specialized knowledge will have to be obtained to complement the sound basic training of the good internist. It may be that the physician's attitude toward the potentialities of his older patients will need enlightenment. This can be obtained by visiting those centers where no preconceived limits are put on the functional recovery of the patient, and where the results of vigorous, enthusiastic treatment indicate that from 40 to 70% of even those older patients who have been disabled for long periods of time can be restored to complete self-care.[6] This is a challenge to every internist to improve these services and continually to improve these results.

SUMMARIO IN INTERLINGUA

Le discussion accentua le rolo del internista in le servicios restaurative que medicos e altere expertos technic e professional de campos vicin provide pro meliorar o al minus pro mantener le capacitates physic e functional de patientes qui es chronicamente malade. Le termino *servicios restaurative* pare plus appropriate que *rehabilitation,* proque iste ultime termino se associa usualmente con objectivos vocational, e tales es generalmente minus significative pro personas de etate avantiate.

A causa del continue augmento del numero de personas de etate avantiate e a causa del competentia special del internista in le diagnose e le tractamento de un extense spectro de morbos, il es a expectar que le internista va trovar se confrontate de plus in plus frequentemente con le problemas medical del population de etate avantiate. Usque nos trova le medios pro le curation de multes del maladias chronic, le medico debe servir se de mesuras que reduce in tanto que possibile le invaliditate que ha resultate in nostre patientes ab ille maladias.

Restaurative servicios medical, initiate le plus promptemente possibile post le declaration del morbo, pote contribuer de maniera significative al reduction o prevention de residuos de invaliditate. Un tractamento energic e enthusiastic es capace a restaurar a statos de complete autonomia mesmo ille patientes de etate avantiate in qui le invaliditate es un condition de ancian duration.

BIBLIOGRAPHY

1. Perrott, G. St. J., Smith, L. M., Pennell, M. Y., and Altenderfer, M. E.: Care of the long term patient, Source Book on Size and Characteristics of the Problem, Public Health Service Publication No. 344, U. S. Department of Health, Education and Welfare, Public Health Service, 1954, U. S. Government Printing Office, Washington 25, D. C.
2. Special Health Services Fact Book, U. S. Department of Health, Education and Welfare, Public Health Service. (Not available for general distribution.)
3. Guides to Action on Chronic Illness, 1956, National Health Council, New York, N. Y.
4. Dacso, M. M.: Clinical problems in geriatric rehabilitation, Geriatrics **8**: 179–185 (Apr.) 1953.
5. Buchanan, J.: Rapid mobilization of cerebrovascular accident patients, Arch. Physical Med. and Rehabil. **37**: 150–151 (Mar.) 1956.
6. Ferderber, M., and Hammel, G.: An effective comprehensive program for geriatric patients, J. A. M. A. **157**: 407–413 (Jan. 29) 1955.

RHEUMATOID SPONDYLITIS: A CLINICAL AND SOCIO-ECONOMIC STUDY *

By ROBERT L. SWEZEY, M.D., *Los Angeles, California,* JAMES PATTERSON, M.D., *San Diego, California,* STANLEY MARCUS, M.D., *Sherman Oaks, California,* DAVID STRANGE, M.D., *Castro Valley, California,* and MELVIN H. LEVIN, M.D,. *Beverly Hills, California*

THE purpose of this paper is to describe the clinical manifestations of rheumatoid spondylitis and its impact upon the social and economic life of the individual. Inferences as to its precise relationship to other arthritic and collagen diseases will be left to the reader and future investigators. The exact characterization of the disease which we in the United States choose to call "rheumatoid spondylitis," and which in Europe is generally referred to as "ankylosing spondylitis," [1] has been a subject of contention for many years.

HISTORY

The first reported description of what we now recognize as rheumatoid spondylitis was by Bernard Conner in 1691. Our present day interest stems from the papers by von Bechterew in 1893, Strümpell in 1897, and Marie in 1898. Schmorl, in his classic study of 10,000 spines, found eight cases of rheumatoid spondylitis.[2] The first large series in American literature was the report of 100 cases by Boland and Present in November, 1945.[3] Polley's monumental study of 1,035 cases in 1946 has provided a frame of reference for all subsequent clinical work in this field.[4]

PATHOLOGY

Our present knowledge of the pathologic changes in rheumatoid spondylitis is based largely on data obtained from about 50 autopsies of advanced cases, and in the last decade the addition of reports of biopsy material from peripheral joints in about an equal number of cases.[5, 6] Collins reports the sole study of the sacro-iliac joints in this disease. He observed in an advanced case a bland, partly bony, partly fibrous union of the sacrum and ileum with enclosed islets of articular cartilage in the adhesive bands, as well as an irregular advance of ossification from either side of the joint surfaces.[7] In a recent study of biopsied nonarticular spine, perispinal tissue and peripheral joint tissue, Yden et al. have again called attention to the endarteritis obliterans occurring in the synovia of diarthrodial joints. This lesion was

* Received for publication December 10, 1956.

From the Wadsworth General Hospital, Veterans Administration Center, Los Angeles, and the Department of Medicine, Medical Center, University of California, Los Angeles.

Requests for reprints should be addressed to Robert L. Swezey, M.D., 10911 Weyburn Avenue, Los Angeles 24, California.

unrelated to x-ray therapy.[5, 6] They describe new bone formation occurring not only on the surfaces of the spinous processes, but also as lamellae between the interspinous ligament and the muscular and fatty tissues. This corresponds to Collins' findings that paravertebral ligamentous calcification and ossification develop in the outer lamellae of the annulus fibrosus rather than in the ligaments per se.[7] The classic concept of typical villous formation in the diarthrodial joints of the spine is based on very little data. Van Swaay has recently challenged this concept after careful study of three cases in which he found the joint spaces to be filled with proliferating cartilage which became secondarily calcified and then ossified.[8] Cruickshank, in his study of peripheral joint disease in 12 cases of rheumatoid spondylitis, felt that "despite many similarities, because of the slightly greater tendency to hemorrhage, thickening of small vessels, and bony fusion in the peripheral joints of patients with rheumatoid spondylitis, the changes could not be considered to be due to the same process as true peripheral rheumatoid arthritis.[6]

The proved case of a rheumatoid nodule in a vertebral body reported by Baggenstoss, Bichel and Ward in a patient with peripheral rheumatoid arthritis is of great interest;[9] the three additional cases which they report as suspicious by x-ray in patients with definite rheumatoid spondylitis probably represent manifestations of the anterior vertebral osteitis which Romanus and Yden have recently described.[10, 11] These latter authors cite x-ray evidence of disc degeneration in 40% of their 250 cases, frequently documenting this with nucleograms.[11] This is in contrast to the generally held concept that the intervertebral discs escape pathologic changes.[2, 35]

Definition

Rheumatoid spondylitis is a systemic disease which characteristically involves the spine in young men with painful ankylosis. The manifestations may range from a painless stiffening of the spine or occasional "sciatica," on the one hand, to a severe wasting, painfully deforming kyphoscoliotic spinal disease with severe iritis and secondary amyloidosis. Most patients who have had the disease for six months will demonstrate bilateral roentgenographic evidence of sacro-iliac disease.[11] Only rarely will sacro-iliac changes be absent in cases of over five years' duration.[4] The syndesmophyte formation in the perispinal ligaments, which in its most advanced form produces the picture of the so-called "bamboo" spine, is a later and less regular finding.[12] The presence of bilateral sacro-iliac disease documented by appropriate x-rays is almost invariably present in rheumatoid spondylitis and is considered an essential diagnostic feature.[2, 4, 11, 12]

Material

In the clinics and on the wards of the Veterans Administration Center, Los Angeles, California, we have had an opportunity to observe some 300 cases of rheumatoid spondylitis, of which 100 were available for this review.

We have observed in our cases what amounts to a composite of the usual and the rare manifestations of this syndrome and, in addition, have made observations of its socio-economic impact.

The 100 cases chosen for this study represent a selected series by virtue of the fact that all were veterans of World War I through the Korean War, and were necessarily in reasonably good health prior to their enlistments. All the cases had definite bilateral sacro-iliac changes by x-ray. The proximity to the Veterans Administration Hospital, the interest of the patients in seeking Veterans Administration care, the fact of their current follow-up status or their admission to the hospital for a problem related or unrelated, and other unknown factors, all tended to weight this series generally in the direction of a predominance of males in lower income brackets with fairly severe disease.

Methods

A standardized form was established in which a complete history of the rheumatic disease was obtained, and the physical, laboratory and x-ray findings were systematically recorded. The patients were asked to answer all of the questions pertaining to the medical and sociologic history, and then all of these answers were subjected to evaluation by one of us in order to ascertain the exact meaning of the answers and to clarify the questions. In this manner, additional data not specifically requested could be obtained. A complete medical examination was then performed and the pertinent laboratory and x-ray data were obtained.

Data

These patients ranged in age from 18 to 79 years, with an average age of 37.7 years. The age at onset was from 10 to 69 years, with an average of 25.6 years. The average duration of illness was 11.8 years. The average duration of follow-up is 3.7 years. Thirty-four cases were followed over five years, 23 cases were followed from three to five years, 23 cases were followed from one to three years, and 20 cases were followed for less than one year.

An attempt was made to evaluate possible *precipitating factors.* In 30 cases none was felt to be significant. Several listed more than one factor. In 22 cases, symptoms of spondylitis seemed to be related to an episode of severe trauma involving the spine. Twenty cases attributed their onset to excessive fatigue, 25 to exposure, 13 to infection, and 11 to emotional stress. Only two of these patients had a history of presumed gonorrhea immediately antedating their spondylitis. In one other case nonspecific urethritis antedated the onset of rheumatoid spondylitis.

Initial Symptoms

The initial symptom in 66 cases was pain, in 12 it was stiffness, in three it was generalized fatigue, and in 19 it was a combination of these. The

TABLE 1

Location of Initial Symptoms

	All Cases
Sacro-iliac	25
Lumbar	35
Dorsal	9
Cervical	1
Multiple back symptoms	4
Back and peripheral joint	4
Large peripheral joint	14
Small peripheral joint*	8

* Metatarsal-phalangeal, metacarpal phalangeal, and interphalangeal joints.

pain or stiffness refers to the spine and does not apply to the symptoms of the peripheral onset when that antedated the spondylitic syndrome.

On the basis of symptoms only, at the time of the study, there were 18 cases with disease limited to the spine, 52 with hip involvement, 14 with shoulder involvement, and 54 with involvement of joints more peripheral than the hips and shoulders. Of our total group, 79 cases had neck symptoms, 90 dorsal spine, and 100 lumbar spine or sacro-iliac symptoms.

FAMILY HISTORY

There was a history of typical rheumatoid arthritis in the immediate family in 17 cases, and of rheumatoid spondylitis in five cases. There were, in addition, six cases of probable rheumatoid spondylitis. In seven cases there was more than one member of the immediate family with either rheumatoid arthritis or rheumatoid spondylitis. This includes one pair of brothers in this series. In one case a twin brother was thought to have spondylitis, but he was not available for examination.

SYSTEMATIC MANIFESTATIONS

Systemic manifestations usually associated with rheumatoid spondylitis are listed in table 2. In addition, there were five cases of generalized lymphadenopathy, two with splenomegaly (in one of these this was transient, associated with an acute attack of peripheral rheumatoid arthritis). One patient with severe peripheral involvement had typical (biopsy confirmed) rheumatoid subcutaneous nodules about the extensor surfaces of the elbows.

TABLE 2

Symptoms of Systemic Disease

Fatigue	90
Chest pain*	77
Excessive perspiration, general	74
of hands only	5
Weight loss†	56
Iritis, total attacks	33
(Attacks associated with flare of rheumatoid spondylitis)	19
Psoriasis	5
Exacerbated with back symptoms	3

* Chest pain of varied causes.

† In 33 of the 56 cases the weight loss was greater than 20 pounds. The greatest weight loss, which was explicable on the basis of rheumatoid spondylitis alone, was 60 pounds.

One patient had a typical patch of chronic discoid lupus erythematosus on the forehead. This was confirmed by biopsy. The L.E. cell preparations were negative.

The *interval from onset* of symptoms to the establishment of the diagnosis of rheumatoid spondylitis was less than one year in 44 cases, less than two years in 11 cases, less than three years in five cases, less than four years in six cases, five to 10 years in 21 cases, and longer than 10 years in nine cases. The longest interval from onset to diagnosis was 27 years.

Prior to the establishment of the diagnosis of rheumatoid spondylitis, no diagnosis had been made in 36 cases. The diagnoses made, in order of their frequency, were: back strain in 12, rheumatism or arthritis in 12, "disc" in seven, "nothing wrong" in six, spinal trauma in five, congenital deformity of spine in four, and "nerves" in three. There were, in addition, one case each in which the following was diagnosed: Reiter's disease, "spur," "weak hips," tuberculosis of the spine, gout, decalcified spine and "broken arches."

There were 13 patients in this group who had definite evidence of organic *heart disease*. One case had had two myocardial infarctions. One had diabetes mellitus, congestive failure, and a murmur of mitral insufficiency. One had an apical systolic murmur and electrocardiographic evidence of cor pulmonale. Three had aortic insufficiency and congestive failure. Of these, two had a history of rheumatic fever and all three gave a history of peripheral rheumatoid arthritis and iritis. Two had mitral insufficiency. One of these had a history of rheumatic fever and iritis, and both gave a history of peripheral rheumatoid arthritis. Four cases had had an acute rheumatic fever-like syndrome during adult life associated with a prolonged P-R interval in three cases, and a gallop rhythm plus abnormal T waves in the fourth.

There were *genitourinary* tract symptoms in 30 cases. In order of frequency of occurrence as individual cases, they were: dysuria in eight, nonspecific urethritis in four, nephritis in three, renal calculi in three, prostatitis in three, gonorrhea in two, nocturia in two, hydronephrosis in two, "kinked" ureter in one, ectopic kidney in one, and uremia in one. Of the three cases of urethritis, two had Reiter's syndrome and one had conjunctivitis and urethritis without peripheral arthritic symptoms.

Symptoms of *gastrointestinal disease* were present in eight cases. Three had a proved duodenal ulcer, one had had an episode of hematemesis of unknown cause, and one had had a diagnosis of gastritis made in the past. In addition, there was one case with terminal ileitis, one with a spastic colon, and one with a nondescript indigestion of undetermined cause.

Among the other diagnoses in these patients, the following were of interest: two cases of psychosis, and one case each of bronchiectasis (antedated spondylitis), pleurisy, and myositis ossificans. There was no case of lymphoma.

Physical Examination

Atrophy of the perispinal muscles was present in 92 cases. *Flattening* of the lumbar curve was noted in 91. The *chest expansion* at the time of the survey was measured, with the results listed. This included a fair number who had increased their chest expansion by virtue of previous deep breathing exercises. In two cases it was not measured. Twenty-five patients had a chest expansion greater than 2.5 inches. Fifty-two had expansions measuring from 1 to 2.5 inches, and 21 had chest expansions of from 0 to 1 inch. *Flexion to the floor* was measured and found to be 100% in 18 cases, less than 6 inches in 16, from 6 to 12 inches in 24 cases, from 12 to 18 inches in 20 cases, greater than 18 inches in 19 cases, and not measured in three cases. There was tenderness on palpation over the spine or sacrum in 23 cases at the time of the survey, and records showed this in previous examinations in five additional patients. There was objective evidence of cervical spine involvement in 72 cases, of dorsal spine in 83 cases, and of lumbar spine in 92 cases.

Table 3

Peripheral Joint Involvement by Physical Examination

	Cases (Not Joints)
Hip joint	39
Joints other than hip	52*
Axial: temporomandibular	2
sternoclavicular	2
shoulder	12
Large nonaxial (knee, ankle, elbow, wrist)	12
Small nonaxial (m.p., m.t., p.i.p.)	24

* In this chart cases only are represented. Cases with more peripheral involvement may have had additional involvement of joints higher on the chart, but these are not listed, as the purpose here is to show the degree of appendicular joint involvement and to emphasize the number of cases with typical peripheral rheumatoid-like involvement.

The peripheral joint involvement is illustrated in table 3. The significant totals here are 12 cases with large nonaxial and 24 cases with small nonaxial joint involvement, or 36 patients with nonaxial peripheral joint involvement.

Four patients in this series had completely normal physical findings. Four others had no objective abnormality of the spine, but had severe peripheral rheumatoid arthritis.

X-Ray

All of the patients in this group had definite evidence of sacro-iliac disease bilaterally, and all of the x-rays were reviewed by at least two of the authors. Sixteen of these cases had the typical "bamboo" spine. Fourteen demonstrated "whiskery" bony proliferation about the pelvis. Eight patients had severe vertebral osteoporosis; however, one of these was a paraplegic from cervical fracture and another had been on prolonged

steroid therapy. Five cases demonstrated definite involvement of the symphysis pubis, with changes similar to those seen in the sacro-iliac joints.

There were seven cases with unilateral hip involvement and nine more with bilateral roentgenographically demonstrable hip disease. Three patients had acrylic hip prostheses, one had bilateral femoral neck amputations, two had had lumbar osteotomies, and one, an exploratory laminectomy. One patient had a healed fracture of the third cervical vertebra (the paraplegic above).

Peripheral joints were x-rayed in 56 cases, with demonstrable changes manifested in 31 cases listed in the table.

The following *laboratory* data were obtained. The most recent Wintrobe sedimentation rate was greater than 10 mm./hr. in 76 cases. A mild anemia characterized by a hematocrit of less than 40 vol.% or a hemoglobin less than 13.0 gm. was present in 54 cases. An anemia of less than 10.0 gm. was seen in two other cases, one with rheumatoid spondylitis alone and one with rheumatoid spondylitis plus Reiter's syndrome. There was mild

TABLE 4

Peripheral Joint Involvement by X-Ray

ARA, grade	Shoulder	Sterno-clavicular	Temporo-mandi-bular	Acromio-clavicular	Elbow	Wrist	Knee	Ankle	M.P. M.T. P.I.P.
I	1	0	0	0	1	1	8	7	10
II	1	0	2	1	0	1	1	2	1
III	0	0	0	0	0	0	0	1	4
IV	0	1	0	1	0	0	0	0	0
Totals	2	1	2	2	1	2	9	10	15

pyuria (5 to 10 white blood cells per high power field) in six patients. Ten cases had more significant urinary findings, ranging from moderate to severe microscopic pyuria and/or hematuria. Only four of these patients had albuminuria ranging from 1 plus to a trace. In all but one of these it could readily be explained on the basis of known uropathy, or congestive failure. In the remaining case of advanced, long-standing rheumatoid spondylitis, a trace of albumin and 12 white blood cells were noted once. No Congo red study was done.

Thirty-two of these patients had at least one *electrocardiogram,* and in 10 cases there were definite abnormalities. In eight of the 10 there were other objective cardiac findings. In the two remaining cases the abnormalities were transient, having occurred during acute exacerbations of peripheral joint disease.

SOCIO-ECONOMIC

Eighty-eight patients out of the total group had had their disease for at least eight years and were evaluated for the socio-economic study.

TABLE 5
General Types of Employment

	Desk	Student	Light Manual	Heavy Manual	Unemployed
Employed					
full-time	20	4	28	1	30
part-time	4	0	2	1	0
Self-employed					
full-time	3	0	5	1	0
part-time	1	0	0	0	0
Total	28	4	35	3	30

Table 5 shows the general types of employment of the entire group. For the purposes of this study, part-time work is defined as from 10 to 30 hours per week. Light manual labor includes truck driver, housewife, assembler, gateman, house painter, carpenter, waiter, welder, clothes cutter and T.V. repairman.

These 88 patients were divided into three groups. Group I consisted of 18 cases who were never unemployed for over three months because of symptoms related to their rheumatoid disease. Group II consisted of 37 cases who were temporarily totally disabled (disabled over a period of three consecutive months) and who at the time of the survey were employed. Group III consisted of 33 patients who were unemployed at the time of the study. The authors are aware that this classification is arbitrary, but it proved most advantageous for the evaluation of our data.

Table 7 shows the minimal, maximal and mean time lost in months during the first 13 years of the illness in each group.

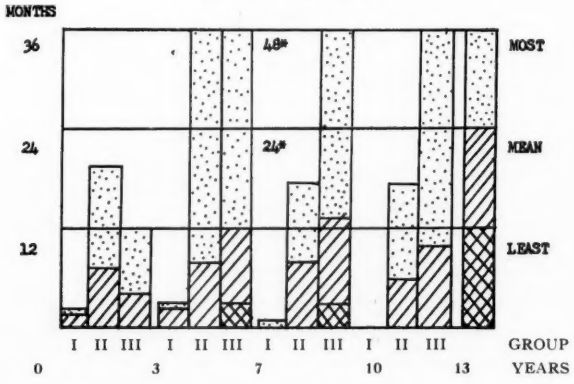
Table 8 lists some of the gross social adjustments made by each group. The data on those who were unable to pass a preëmployment physical examination were volunteered by the patient; all other data are the result of direct questioning. The phrase "major change in social life" denoted significant changes in social and sexual relationships.

TABLE 6
Peripheral Arthritis and Iritis

Extent of Involvement	Group I All Cases	(Iritis)	Group II All Cases	(Iritis)	Group III All Cases	(Iritis)
Spine alone	8	0	9	6	4	1
Spine plus:						
other axial joints	2	0	3	0	0	1
large peripheral joints	3	3	9	3	0	0
small peripheral joints	4	0	0	0	4	2
large and small peripheral joints	2	0	13	6	11	6
hips	0	0	3	1	6	2
Total iritis		3		16		12

TABLE 7

Time Lost from Work



* Figures adjusted for four-year intervals.

In table 8 we have correlated the influence of peripheral joint disease and iritis in the three groups.

In Group III it was arbitrarily estimated that at least four patients were capable of full employment and an additional 12 could work part-time. Of the men in Group III who were on pension, 18 had pensions classified as 100% service connected or $181.00 minimum per month to $237.00 maximum with four dependents. Eight others drew pensions of less than that amount, usually from $17.00 to $75.00 per month. The remaining 17 men in Group III who were physically unable to work at the time of the study included a few who were temporarily hospitalized. A subsequent study of this group revealed that three are now working full-time and two others are capable of doing so. Four of these 17 men are now capable of part-time work. Of the eight who remain physically unable to work, none is limited by virtue of his spinal involvement. This group includes three patients with aortic insufficiency, two with severe peripheral rheumatoid arthritis (one of whom is also crippled by chronic osteomyelitis), one with

TABLE 8

Gross Socio-Economic Adjustments

Group	I	II	III
Major change in career plans	10	26	27
Decreased earning	8	28	28
Increased earning	0	2	0
Unable to pass physical	2	1	2
Major change in social life	3	8	8
Total job changes	46	128	98
Job changes due to rheumatoid spondylitis	10	73	73

TABLE 9
Effect of Treatment on Ability to Work

Modality	Group I	Group II	Group III
X-ray	6/17*	13/47	1/21
Systemic steroid	1/2	5/7	4/11
Conservative	1/18	3/36	4/27
Butazolidin	0/1	1/7	0/5
Gold	0/0	1/5	0/7
Surgery	0/0	1/1†	2/6‡

* 0/0 indicates the cases benefited over the cases treated.
† Lumbar osteotomy.
‡ Bilateral femoral cup arthroplasties.

a detached retina, and one paranoid schizophrenic. One patient died of arteriosclerotic heart disease.

Table 9 shows the effect of various treatments on the patient's ability to work. Each number indicates the number of patients that felt that the modality of therapy was the instrumental factor permitting him to resume work, when previously he had been unable to.

A further attempt to assess the patients' subjective evaluations of the benefits of the various modalities offered is listed in table 10. Conservative therapy is defined for our purposes as therapy given under the supervision of the Physiotherapy Department of the Veterans Administration Hospital in conjunction with large doses of salicylates and rest programs, including hospitalization for bed-rest and other physiotherapy when indicated.

TABLE 10
Subjective Evaluation of Therapy

	Group I			Group II			Group III		
	Good	Fair	Poor	Good	Fair	Poor	Good	Fair	Poor
X-ray* Course 1	9	2	2	8	7	11	1	3	10
Course 2	3	1	0	4	10	2	1	1	2
Course 3	0	0	0	0	2	3	0	0	2
Systemic steroid	0	2	0	4	2	1	1	5	5
Conservative	3	13	2	14	20	2	3	21	3
Butazolidin	0	0	1	3	3	1	2	3	0
Gold†	0	0	0	1	1	3	0	0	7
Surgery	0	0	0	1	0	0	0	4	2
None	1	—	—	1	—	—	1	—	—

* Thirteen cases in Group I, 26 cases in Group II, 14 cases in Group III treated by x-ray.
† Treated elsewhere.

Discussion

Because we were dealing with a veteran population, the predominance of males over females in our series is 99:1, rather than the usual approximate 10:1.[1, 2, 4, 12, 28] The predominance of males with rheumatoid spondylitis as opposed to the high incidence of females with classic peripheral rheumatoid arthritis has often been cited as evidence that the two processes are separate.[2–13] Tyson's interesting observation that the incidence of chronic alcoholism is much higher in men than in women, while Korsakoff's syndrome occurs in a ratio of seven females to one male,[14] bears repeating in this regard, i.e., the rheumatoid state possibly is the common denominator, with peripheral manifestations more common in females, spondylitis more common in males.

Most of the studies of rheumatoid spondylitis have revealed a significant *family history* of rheumatoid spondylitis as well as peripheral rheumatoid arthritis.[12, 15, 16, 31] But Polley in his large series found a family history of rheumatoid spondylitis in only 0.4%. There was a definite history of rheumatoid spondylitis in five of our cases, and it was probable in six more. It was suspected in one pair of twins but could not be confirmed. In the immediate family of 17% of our patients, there were cases of typical peripheral rheumatoid arthritis.

We were impressed with the extremely low incidence (two cases) of a *history of gonorrhea* in our group. We did not have available, as a rule, the military service health records to document this low incidence of Neisserian infection. Our data are in accord with Polley's findings but contrast with the high incidences reported elsewhere.[2, 4]

The *symptomatology* of this group of spondylitics was fairly typical.[2, 4, 12] The frequency of *fatigability* and *generalized stiffness* as initial or concomitant symptoms bears emphasis. The locus of *initial symptoms* in the dorsal and (in one case) the cervical spine should be noted. Symptoms in the thoracic spine are often accompanied by pleuritic-like pains. Involvement of the 44 costospinal joints of the ribs, as well as the ribs themselves, in what is apparently a perichondritis and arthritis of the costosternal joints may mimic pulmonary or cardiac disease.[1]

Further evidence of the *systemic nature* of the disease is emphasized by the degree of *weight loss,* which was in excess of 20 pounds (and often over 30 pounds) in one third of the cases.

The *anemia* was generally mild. From our data it would seem that if the hemoglobin in a spondylitic is below 10.00 gm. one should look for an additional cause for the anemia.

The incidence of *iritis* in 33% of our cases is high, the usual figure being about 10%.[4, 15, 16, 21] In 10 of our 33 cases with iritis, the spine alone was involved. It has been stated that iritis occurs only in the presence of peripheral joint involvement.[11] Our data indicate that iritis occurs in

patients who generally have a more severe form of the disease, which usually, but not necessarily, includes peripheral joint involvement.

The five cases of associated *psoriasis* reflect the increased incidence of coexistence of these two conditions.[17] The exacerbation of the psoriasis and spondylitis simultaneously in three cases is of interest.

The proved incidence of *peptic ulcer* in our group was 3%. An additional three cases may have had an ulcer. Thus a maximal figure of 6% peptic ulceration can be reached; of these cases, several had been on ulcerogenic medication. This incidence is no greater than that estimated in an otherwise normal male population.[1, 18]

Of our 30 cases with *urinary tract symptoms,* it is notable that many had conditions easily considered as etiologic in back disorders. It is regrettable that appropriate studies of serum and urine chemistries or chemical analysis of the calculi were not done. It is conceivable that the renal calculi were related to the severe decalcifying spinal disease and possibly to periods of bed-rest. It should be recalled in this regard that at one time parathyroidectomies were performed as treatment for rheumatoid spondylitis.[4]

Thirteen patients in our series had definite evidence of *cardiac involvement.* Only one had evidence of cor pulmonale. In regard to the effect of the reduction of chest expansion on the vital capacity, it has been observed that the increased diaphragmatic excursion adequately compensates for the restricted chest motion.[19] No studies of vital capacity were done to confirm or deny this. We suspect that this is true. Those of our patients who were diligent in their chest exercise program showed an objective gain in chest expansion, and had subjective benefit with regard to their ease of breathing.

There was a paucity of *pulmonary complications.* Only one patient complained of "pleurisy," and this may well have been pleuritic pain related to his rheumatoid spondylitis.[2] There was only one case of bronchiectasis, and in this case it antedated the rheumatoid spondylitis. This is of interest in that the reduced chest expansion is supposed to predispose to pulmonary disease.[18, 21] The two patients with suspected arteriosclerotic heart disease may have had cardiac involvement related to the rheumatoid state, i.e., coronary arteritis with clinical and electrocardiographic changes simulating arteriosclerotic heart disease.[20] We found three cases with aortic insufficiency and no evidence of syphilis. This has been described elsewhere as occurring with rheumatoid spondylitis.[12, 21, 31] A more detailed report on the cardiac findings of this group will appear in the future.

The incidence of *peripheral joint disease* is high. In 22 cases it was the initial manifestation. Fifty-two cases had evidence of peripheral joint disease not including the hips, 36 cases had nonaxial joint involvement, and 24 cases had involvement of the small joints of the hands and feet.

Most noteworthy was the degree of permanent changes in peripheral

joints manifested by our patients. Sixteen of the 31 cases with x-ray changes in peripheral joints had changes of grade II or greater intensity. This does not support the usual impression that peripheral joint disease in rheumatoid spondylitis is usually mild and reversible.[4, 8, 14, 21, 31, 33] The experience in the literature with regard to the frequency and type of peripheral joint involvement is variable. In general, a much higher incidence of peripheral joint involvement is found in the series in the American literature.[1, 2, 3, 4, 8, 31, 32] Relative rarity of peripheral joint involvement in most European series represents one of the major reasons for the divergence of opinion as to etiology of rheumatoid spondylitis, and the reluctance of most European authorities to consider "ankylosing spondylitis" as a variant of rheumatoid arthritis.[1, 3, 4, 6, 8, 13, 29]

Worthy of emphasis is the fact that eight patients in our group had normal backs. This figure is almost exactly equal to that found by Blumberg and Ragan in a similar series.[36]

The *"whiskery" bony proliferation* seen about the exterior aspects of the pelvis and upper femurs at the sites of muscle attachments is quite characteristic and can be differentiated from simple roughening of these areas as seen in otherwise normal pelves.[16] At times these "whiskers" have extended as far as an inch from the ischia, anterior superior iliac spines, or femoral tuberosities. This great tendency to bone overgrowth may in part account for the frustrating long-term results of surgical treatment of hip disease in these patients.[10, 16, 39] Tyson found involvement of the *symphysis pubis* with roentgenographic changes similar to those seen in the sacro-iliac joints to occur in 10% of 60 female spondylitics studied.[15] He states that it is a rare finding in males.[15] We observed these changes in 5% of our group of 99 men and one woman. In one patient this was associated with local pain and tenderness.

Traumatic *fracture of the cervical spine* is a hazard. Our case suffered his fracture in a fall at home. Chiropractic manipulation and intratracheal intubation at surgery are potentially hazardous to these patients.

Despite the recent well documented series showing a high incidence of *amyloidosis* in rheumatoid arthritis, the usual clinical and laboratory studies failed to indicate its presence.[26, 27, 28] Albuminuria (the most common finding in secondary amyloidosis [28]) was present in only four cases, and in three of them it could be explained on a basis other than amyloidosis. One of our patients with rheumatoid spondylitis (not included in this series) died of amyloidosis several years before this series was compiled.

One patient in our series had definite *subcutaneous nodules* of the variety and location typical for peripheral rheumatoid arthritis. The biopsy of one of these nodules was consistent with a rheumatoid nodule. This patient had chronic osteomyelitis of one leg, severe peripheral rheumatoid arthritis, advanced hip disease, fused sacro-iliac joints and almost normal back motion, with no evidence of higher spinal involvement by x-ray. It is conceded that

a rheumatoid nodule in a patient with typical rheumatoid spondylitis is extremely rare.[9, 10, 11, 15, 16, 30, 31, 38] They have been reported rarely in atypical cases of rheumatoid spondylitis.[16, 30] Our patient with a nodule would be considered an atypical case of rheumatoid spondylitis.

It is clear from our data that the patients in Group I generally had mild disease, no hip involvement, little iritis, and little peripheral joint involvement. Two of these patients had typical "bamboo" spines, and three others had marked "ligamentous" calcification approaching "bamboo." One of the patients with a "bamboo" spine had had severe spinal flexion deformities, which were largely relieved after about one month of corrective exercise and traction. By the above criteria the patients in Groups II and III had more severe disease. The increased incidence of hip involvement in our Group III correlates well with the generally stated experience that progressive hip involvement, rather than the degree of spine involvement, seems to be the most significant determining factor in a given patient's ability to make a satisfactory economic adjustment.[31, 37] It is equally true that in a given case, severe peripheral joint involvement other than the hips may be the limiting factor in a patient's *socio-economic* adjustment. But this is not so regularly predictable as hip disease. Not one of the cases in Group I had objective evidence of hip involvement at the time of our survey.

The majority of our patients in all groups felt that the effect of their disease was to reduce their earning potential. Errors and delay in diagnosis may have added to the burdens of the disease. Because of additional education, or a more skilled type of work indirectly resulting from adjustments to the disease, two patients felt that their earnings were greater than might have been the case. In the evaluation of these data, the possible influence of pensions must be kept in mind.

Because of the nature of the back involvement, systemic manifestations and the notorious tendency for patients with rheumatoid disease to "gel" after prolonged immobility, it was our impression that most of these patients adjusted best to a *type of employment* which did not demand heavy lifting, undue exposure or fatigue, prolonged sitting (including driving) or standing. Those patients who were self-employed or whose jobs permitted freedom of mobility or permitted them to work on their own seemed best adapted to the limitations imposed by this disorder.

It has been stated that about 75% of patients with rheumatoid spondylitis can lead a fairly normal life.[31, 36] These figures have been compared to 37% of patients with rheumatoid arthritis.[31] Since criteria for diagnosis vary for both syndromes, it is difficult to make such an estimate. As indicated earlier, our series tends to be weighted in the direction of more serious disease and greater economic need than the anticipated average. Although 31 patients were unemployed at the time of the survey, a closer appraisal reveals that only eight are *totally disabled* (including one who had arteriosclerotic heart disease and died at home without autopsy). None of the

patients was disabled solely by his spinal involvement. Two were incapacitated by severe peripheral joint involvement.

It was hoped that our data as graphed in table 7 would indicate that after a given period of time one could predict that a patient with severe disease could plan to be reintegrated into a useful life built around whatever residual deformity he might have. While this certainly is true in individual cases, it is not predictable. The data suggest only that the patients in Groups I and II by and large suffered the severest manifestations of their disease by the end of the seventh year.

While only 23% of the patients treated with x-ray and/or conservative therapy were returned to work, and 50% of those treated with systemic steroids were so benefited, the discrepancy in the number of patients treated by x-ray (85) compared to steroids (20) must be kept in mind.

Evaluating subjective data on the treatment of arthritis is notoriously hazardous. Our data in tables 9 and 10 suggest that the most successful modality is x-ray therapy. Conservative therapy was less dramatic, but definitely helpful for most patients. Steroids and Butazolidin were about as successful as conservative therapy in the small number of cases treated with these drugs. The data do not indicate that 50% of the patients with a good subjective response to Butazolidin had to discontinue its use because of toxicity.

Our usual *program of treatment* consists of a maximal trial of conservative therapy, followed by one to three courses of x-ray therapy for relief of pain in the event the former is unsuccessful. We concur with the conclusions of Brown and Abbatt [34] on the results of their preliminary study of leukemia in spondylitics treated by x-ray, that the suggested slight increase of leukemia in such patients is so minimal that it leaves unaltered the indication for x-ray therapy. If a patient is refractory to the above modalities, then Butazolidin is tried with the patient under close observation for evidences of toxicity. It should be made clear that our hope with present modes of therapy is relief of pain and prevention or correction of deformities. No known modality of therapy arrests this disorder.

Summary and Conclusions

1. The clinical and socio-economic data on 100 cases of rheumatoid spondylitis from a Veterans Administration hospital are reported. They presented practically all of the known clinical manifestations and complications of the disorder.

2. In most cases the disease caused significant socio-economic dislocation, but in general most patients were able to be self-sufficient and to live a full, if limited, life.

3. The degree of spinal deformity was not found to be of great importance from the standpoint of socio-economic adjustment. Small periph-

eral joint and cardiac involvement contributed to the greatest disability. The development of hip disease was an unfavorable prognostic sign.

4. Patients with rheumatoid spondylitis are most successfully employed in occupations in which they can frequently change from a sitting to a standing position, where heavy manual labor is not required, and where, ideally, they can have one or two periods of rest of at least 30 minutes during the working day.

5. Many patients can be well managed on a conservative regimen. X-ray therapy gives the best relief of sustained back pain. Phenylbutazone, steroids and other antirheumatic agents may be of value in selected cases.

6. A hemoglobin of less than 10.0 gm. rarely occurs in uncomplicated cases of rheumatoid spondylitis, and other causes should be searched for if such a value is found.

Summario in Interlingua

Esseva studiate 100 casos de spondylitis rheumatoide in un hospital del Administration de Veteranos. Un tertio del casos esseva tenite sub observation durante plus que cinque annos. Le characteristicas clinic es describite e discutite in detalio. Dece-tres casos exhibiva objective anormalitates cardiac. Trenta-sex casos monstrava objective affectiones de nonaxial articulationes peripheric. Un historia familial de arthritis rheumatoide esseva trovate in le familia immediate de 17 casos e de spondylitis rheumatoide in illo de cinque casos.

Un historia de gonorrhea esseva trovate in solmente duo casos. Le absentia de complicationes pulmonar esseva notabile. In un caso que esseva atypic, nodulos rheumatoide esseva provate per biopsia. Le serie includeva un caso de chronic lupus erythematose discoide. Nivellos de hemoglobina de infra 10 g esseva trovate in solmente duo casos.

Es sublineate le periculo de fracturas spinal, specialmente cervical. Le studio socio-economic revelava que le majoritate del patientes con morbo spinal sol non experientiava alte grados de incapacitate general. Morbo cardiac e morbo de articulation peripheric esseva responsabile pro le plus alte grados de incapacitate. Le disveloppamento de morbo coxal esseva un disfavorabile signo prognostic. Le duration del morbo non merita confidentia como indice prognostic.

Le majoritate del patientes respondeva ben a un regime conservative e profitava ab le therapia radiologic. Leve formas de travalio in occupationes que permitteva le libere intercambio de positiones sedentari e erecte esseva le plus satisfactori. Un desiderato es un o duo periodos de 30 minutas de reposo per die.

BIBLIOGRAPHY

1. Hart, F. D.: Ankylosing spondylitis, Ann. Rheumat. Dis. **14**: 77, 1955.
2. Hollander, J. L., Editor: Comroe's Arthritis and allied conditions, 5th Ed., 1953, Lea & Febiger, Philadelphia, p. 548.
3. Boland, E. W., and Present, A. J.: Rheumatoid spondylitis: study of 100 cases and references to diagnostic criteria, J. A. M. A. **129**: 843, 1945.
4. Polley, H. F.: Rheumatoid spondylitis: a study of 1,035 cases, read at American Rheumatism Association meeting, New York, May 24–25, 1946.
5. Engfeldt, B., Romanus, R., and Yden, S.: Histological studies of pelvo-spondylitis ossificans (ankylosing spondylitis) correlated with clinical and radiological findings, Ann. Rheumat. Dis. **13**: 219, 1954.

6. Cruickshank, B.: Histopathology of diarthrodial joints in ankylosing spondylitis, Ann. Rheumat. Dis. **10**: 393–404 (Dec.) 1951.
7. Collins, D. H.: The pathology of articular and spinal diseases, 1950, The Williams & Wilkins Company, Baltimore, p. 315.
8. Turney, H. F.: Ankylosing spondylitis, "President's Address," Proc. Roy. Soc. Med. **45**: 57, 1952.
9. Baggenstoss, A. H., Bichel, W. H., and Ward, E. C.: Rheumatoid granulomatous nodules as destructive lesions of vertebrae, J. Bone and Joint Surg. **34A**: 601–609, 1952.
10. Romanus, R., and Yden, S.: Destructive and ossifying spondylitis changes in rheumatoid ankylosing spondylitis, Acta orthop. Scandinav. **22**: 88–99, 1953.
11. Romanus, R., and Yden, S.: Pelvo-spondylitis ossificans, 1955, Year Book Publishers, Chicago.
12. Rheumatism and Arthritis (10th Rheumatism Review), Ann. Int. Med. **39**: 590–593 (Oct.) 1953.
13. Buckley, C. W.: Differential diagnosis of spondylitis and treatment of the principal forms, a survey of chronic rheumatic diseases, 1938, Oxford University Press, New York.
14. Tyson, T. L.: Spondylitis ankylopoietica, M. Clin. North America **21**: 1755–1761, 1937.
15. Tyson, T. L., Thompson, W. A. L., and Ragan, C.: Marie-Strümpell spondylitis in women, Ann. Rheumat. Dis. **12**: 40–42 (Mar.) 1953.
16. Hart, F. D.: Ankylosing spondylitis: a survey, Ann. Rheumat. Dis. **13**: 186, 1954.
17. Gribble, M. de G.: Rheumatoid arthritis and psoriasis, Ann. Rheumat. Dis. **14**: 198, 1955.
18. Harrison, T. R.: Principles of internal medicine, 1952, The Blakiston Co., Philadelphia, 1444.
19. Hart, F. D., and Bogdanoviel, N.: Thorax in ankylosing spondylitis, Ann. Rheumat. Dis. **9**: 116, 1950.
20. Levin, M. H., et al.: The heart in rheumatoid arthritis: a clinical-pathological correlation of 43 autopsied patients, presented June 4, 1955, at American Rheumatism Association meeting, Atlantic City, N. J.
21. Blumberg, B., and Ragan, C.: The natural history of rheumatoid spondylitis, Medicine **35**: 1, 1956.
22. Storey, G., and Tegner, W. S.: Paraplegic para-articular calcification, Ann. Rheumat. Dis. **14**: 176, 1955.
23. Gerber, A., and Roab, A.: Vitamin A poisoning in adults: description of a case, Am. J. Med. **16**: 729, 1954.
24. Steinberg, C. L., Gardner, D. E., Smith, F. A., and Hodge, H. C.: Comparison of rheumatoid (ankylosing) spondylitis and crippling fluorosis, Ann. Rheumat. Dis. **14**: 378, 1955.
25. Kaplan, L.: Personal communication.
26. Laine, V., Kauda, V., and Ritana, V. V.: The occurrences of amyloid in rheumatoid arthritis: some observations, Acta rheumat. Scandinav. **1**: 43, 1955–56.
27. Teilum, G., and Lindahl, A.: Significance of amyloid changes in rheumatoid arthritis, Acta med. Scandinav. **149**: 449, 1954.
28. Fearnley, G. R., and Lacker, R.: Amyloidosis in rheumatoid arthritis and significance of "unexplained" albuminuria: a report of eight cases, Brit. M. J. **1**: (May 7) 1955.
29. Forestier, J. F., and Bews, A.: Communicaciones 2 Congreso Reumatologica, Barcelona, 1950, Editorial Scientia, Barcelona, p. 10.
30. Erdstrom, G.: Is spondylitis ankylopoietica an independent disease or a rheumatic syndrome?, Acta med. Scandinav. **104**: 397, 1940.
31. Ragan, C., and Snyder, A. I.: Rheumatoid arthritis, DM (Nov.) 1955.

32. Guest, C. M., and Jacobsen, H. G.: Pelvic and extrapelvic osteopathy in rheumatoid spondylitis, Am. J. Roentgenol. **65**: 760, 1951.
33. Graham, D. C., Fletcher, A. A., and Graham, W.: Rheumatoid spondylitis, *in* Rheumatic Diseases, American Rheumatic Association, 1952, Saunders, Philadelphia, pp. 83–87.
34. Brown, W. M. C., and Abbatt, J. D.: The incidence of leukemia in ankylosing spondylitis treated with x-rays: a preliminary report, Lancet **1**: 1283–1285 (June 25) 1955.
35. Stecker, R. M., Sassaman, W. H., Goodman, J. I., Solomon, W. M., and Dowdell, W. F.: Ankylosing spondylitis: clinical history, radiographic findings, and gross anatomic description of the skeleton of one case, Laboratory Investigation **1**: 469, 1952.
36. Blumberg, B., and Ragan, C.: The natural history of rheumatoid spondylitis, Bull. Rheumat. Dis. **6**: 95–96, 1955.
37. Hart, F. D., Robinson, K. C., Allchin, F. M., and MacLagan, N. F.: Ankylosing spondylitis, Quart. J. Med. **18**: 217, 1949.
38. Herrick, W. W., and Tyson, T. L.: The medical aspect of ankylosing spondylitis (Marie-Strümpell), Ann. Int. Med. **15**: 994, 1941.
39. Milch, H.: Femoral osteotomy in the treatment of Marie Strümpell's disease, J. Internat. Coll. Surgeons **20**: 465–473 (Oct.) 1953.

A FEW NOTIONS INVOLVED IN THE CLINICAL USE OF RADIOISOTOPES*

By GOULD A. ANDREWS, *Oak Ridge, Tennessee*

THIS presentation is designed to define and illustrate some basic concepts that may be helpful to physicians using radioisotopes in diagnostic and therapeutic applications. Nothing to be presented is new, and much of it will seem unnecessarily trite to those experienced in this field. My only qualification for presenting these ideas is that I have personally had a very hard time grasping them, and possibly am familiar with some of the snags.

RADIOISOTOPES DEFINED

A radioisotope might be defined as a special kind of atom which has the property of producing radiations. The radiations are waves, or particles, sent out in all directions as a result of internal changes in unstable, or radioactive, atoms. No effort will be made here to describe what goes on in the atoms to produce these radiations; we shall concentrate upon the radiations themselves.

These radiations are of interest to physicians in two ways. First, they can be detected and measured. Second, when present in large enough quantity, they can damage or destroy tissue. The detectability and measurability of the radiations are the basis for most research and for diagnostic applications of radioisotopes. The ability of the radiations to damage or destroy tissue is, of course, the basis of their therapeutic usefulness.

Most elements have both radioactive and stable forms. The usefulness of radioisotopes is often based upon the fact that the radioactive atoms behave the same, biochemically and metabolically, as stable atoms of the same element. This rule breaks down when we are dealing with certain elements at the beginning of the periodic table where there may be a great difference in atomic weight between a radioactive and a stable isotope of the same element. The most striking example is hydrogen, which has another stable form, deuterium, weighing twice as much per atom, and a radioactive form, tritium, weighing three times as much per atom. The three isotopes of hydrogen vary so much in weight that they do not behave in the same way metabolically; these differences in behavior are given the label of "isotope effect." In spite of such exceptions, the general rule is that the various

* Presented as a Morning Lecture at the Thirty-eighth Annual Session of The American College of Physicians, Boston, Massachusetts, April 10, 1957.

From the Medical Division, Oak Ridge Institute of Nuclear Studies, under contract with the United States Atomic Energy Commission.

Requests for reprints should be addressed to Dr. Gould A. Andrews, Chief of Clinical Services, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee.

radioactive and stable forms of an element behave the same in biologic situations.

The Radiations

Let us focus our attention on the radiations. Figure 1, taken from the work of John H. Lawrence, is an effort to describe these radiations. We shall concentrate our interest on the beta and gamma emissions. Alpha particles travel very short distances in tissue, and are of interest chiefly because they constitute the type of radiation hazard involved with certain long-lived radioisotopes that concentrate in bones. The beta and the gamma emissions are important because they are the chief ones used for diagnostic and therapeutic applications. The beta particles, in general, travel not more than a few millimeters in tissue. (When beta particles are produced there is an accompanying "Bremsstrahlung," or soft x-ray type of radiation which

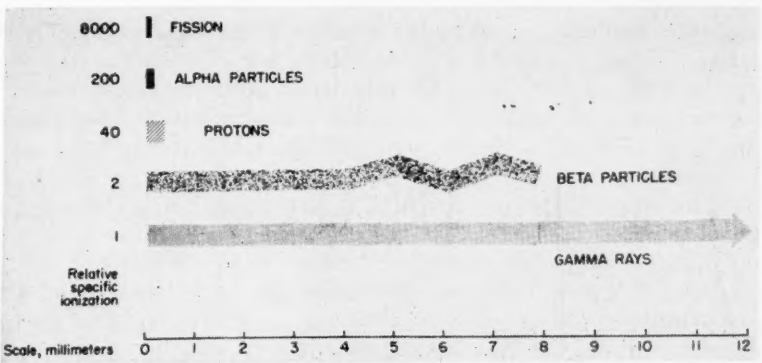


Fig. 1. Penetrating power of rays in centimeter of tissue. (Courtesy of C. A. Tobias and J. H. Lawrence: The clinical use of radioactive isotopes, Bull. New York Acad. Med. **26** (2nd Series): 639–669, 1950.)

can be detected beyond the range of the beta particle. This radiation is not of the right quantity or character to allow easy measurement after tracer doses and is usually unimportant therapeutically. It will be ignored in this presentation.) When isotopes that emit only beta particles are used for diagnostic tests, it is usually not possible to make worth while observations by measuring the radiation emanating from the surface of the body. This is because most of the radiations are absorbed within the tissues. Another feature of the short path of the beta particle is that, in the assay of untreated samples of blood, urine or tissue, much of the energy is absorbed within the sample and does not reach the measuring device; assay of such samples requires special chemical technics to separate the element under study from the surrounding material. The beta particles with higher energy can sometimes be measured in whole tissues and fluids without special treatment. Beta-emitting isotopes are of great importance for internal isotope therapy

because the tissue-destroying effects are limited rather strictly to the special area occupied by the radioactive atoms.

The gamma rays generally travel much farther than the beta particles in tissue and, because of this, interesting and worth while measurements can be made outside the body after tracer doses are administered. For example, the concentration of radioactive chromium in the spleen, after red cells have been labeled with this isotope, may be an index of the splenic breakdown of the cells. Gamma-emitting isotopes also have the advantage that in many instances it is possible to assay tissues and fluid for radioactivity without any special chemical processing. On the other hand, for internal therapeutic applications, many of the gamma-emitting isotopes have such a long path from their source of origin that an effect resembling total-body irradiation may be produced, even if the radioisotope itself is well localized. Therefore, the gamma emissions of isotopes are not often considered of much value for therapy except when the isotope is kept outside of the body—for example, as in a teletherapy device, which allows direction of the beam of radiation into the body. Most radioisotopes produce both beta and gamma emissions, but in varying proportions. This may be of great usefulness, medically, since the gamma emissions can be used for measurements and for detection of the localization of the isotope, while the beta emission may be of use for its therapeutic effect.

Figure 2 summarizes in a simplified form the penetrating ability of these types of emissions. It is important to emphasize that there are great variations within a given class, depending upon the energy with which the particle or wave is sent forth. In the therapeutic use of isotopes in which tissue damage or destruction is the aim, it is, in general, true that the beta- and gamma-emitting isotopes produce essentially the same types of effect; the only important difference is the degree to which the effect is limited to the actual location of the isotope. With the gamma emitters the destructive effect is much more widespread and, for a given energy and half-life, much less intense.

Radioactive Decay and Dose Units

It seems logical, next, to concentrate our attention upon radioactive decay and dose units. Unlike the ordinary stable drugs with which we are familiar, radioisotopes do not have an expiration date on the package. Instead, they have a constantly changing dose value, and our only consolation is that the change in dose occurs in a predictable manner. Any statement about the dose of a radioisotope must include a statement of time to have any meaning. For example, we say that we ordered 100 mc. of gold 198 as of 10 a.m. March 1, 1957; however, on March 2 this will not be 100 mc.; it will be about 77 mc. In clinical work, when no specific statement is made about the time at which the dose is expressed, it is understood that this dose is calculated as of the time of administration to the patient. Usually all measurements obtained at a later date for the same dose are corrected for

radioactive decay back to this starting point. Radioactive decay occurs in a logarithmic fashion. In an isotope with a short half-life—one day, for example—the amount of residual activity may fall by 50% per day. The 50% disintegration is always based upon the residual amount and not upon the initial amount. Thus we may start out with 100% the first day, 50% the next day, 25% the next day, 12½% the next day, and so on. Theoretically we would never reach zero. What actually happens is that eventually the number of atoms left is so small that we are no longer looking at an average of large numbers and the element of chance comes in; at some unpredictable time the last radioactive atom disintegrates and zero activity is left. Before this occurs, the remains of the radioactivity will have become lost in the ever-present natural "background" of radioactivity. The dose of a radioactive isotope is expressed in curies, or one-thousandth of a curie (a

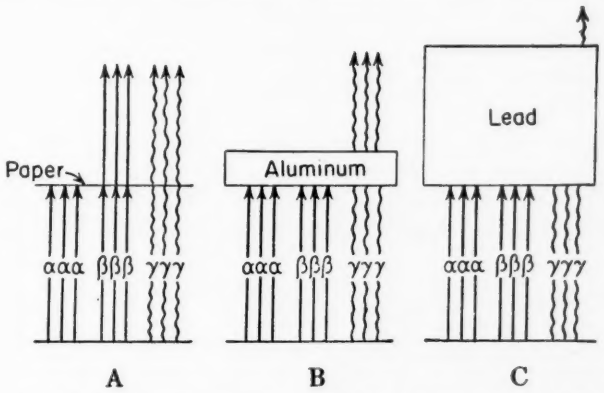


FIG. 2. Relative penetrating power of alpha, beta and gamma radiation.

millicurie), or one-thousandth of a millicurie (a microcurie). These dosage units are based upon a given number of disintegrations per second at the time the measurement is made. The point about this definition that seems to cause the greatest difficulty is the "per second." For some reason many of us have got into the mistaken habit of thinking of the dose unit as representing the total number of disintegrations that will occur in a given sample before complete decay. This is absolutely wrong. The definition specifically states "disintegrations per unit time." Therefore, a millicurie of an isotope with a long half-life, and a millicurie of an isotope with a short half-life, will be producing the same number of disintegrations at the time of measurement. At a later point, of course, the isotope with long half-life will be producing many more disintegrations per unit time than will the isotope of short half-life—that is, more millicuries of the long one will be left. Expressed in a different way (figure 3), the dose represents a point along the decay curve. To think of the dose in millicuries as an expression

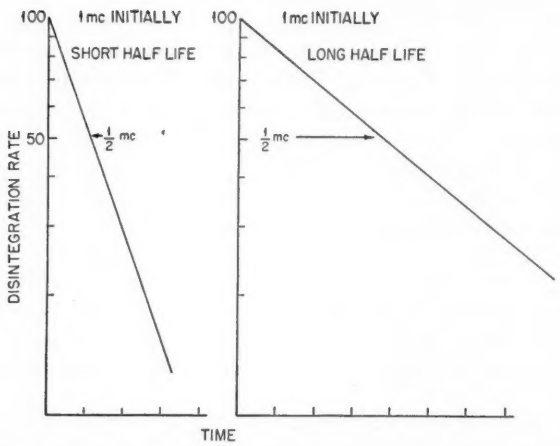


FIG. 3. Representation on semilog paper of disintegration curves for an isotope of a short half-life and one for a long half-life. The quantity in millicuries should be thought of as related to a point on the curve, not to the area underneath.

of the total area under the curve is completely wrong. Based upon a correct understanding of the dose units, it is clear that the amount of radiation delivered to the body, in general, varies directly with the half-life; long half-lived isotopes produce a greater radiation dosage to the tissues, other things

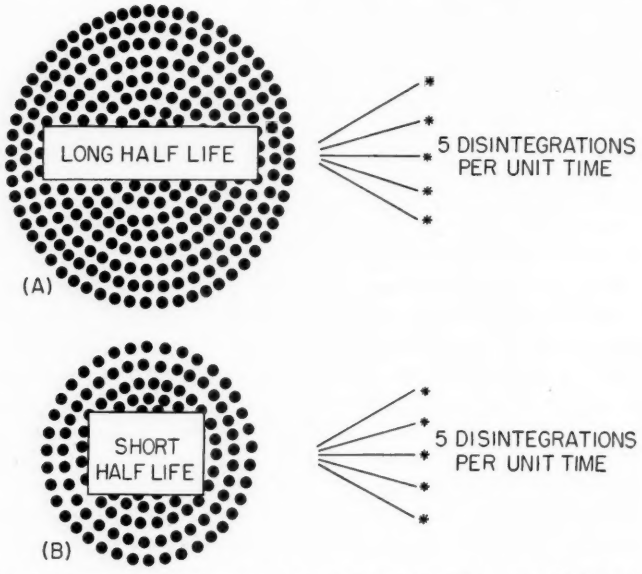


FIG. 4. A and B represent the same number of millicuries. The long half-life element has more atoms, a smaller proportion of them disintegrating each minute.

being equal. These "other things," which would influence tissue dosage, include such factors as the type of radiations, the energies, and the biologic retention of the radioisotope. It should also be obvious that a millicurie of an isotope with a long half-life must include many more atoms than a millicurie of an isotope with a short half-life. This is true because a smaller percentage of the atoms is disintegrating per unit time for an isotope with a long half-life, but the actual number of disintegrations is the same as for the same number of millicuries of the isotope with a short half life. Figure 4 tries to illustrate this point. Assuming that no stable material is present, we find that the total weight of a millicurie of the radioactive isotope with a long half-life would ordinarily be greater than that of the millicurie of the isotope with a short half-life, although the weight per atom of different elements varies with the position in the atomic table. It is to be emphasized that in this diagram all the atoms are unstable until they disintegrate. The fact that only five are shown disintegrating in a given time period interval from the long half-life isotope does not mean that there are any nonradioactive atoms in the sample. They are simply waiting to disintegrate.

Stable Carrier

We do, however, often deal with radioactive atoms in the presence of nonradioactive, or stable, atoms of the same element. This brings us to the concepts of carrier and specific activity. When a sample of a radioactive

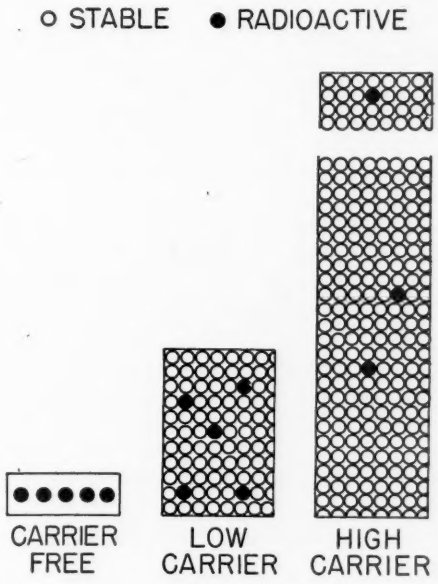


Fig. 5. Representation of samples of a radioisotope with varying amounts of stable carrier.

isotope exists in the absence of any stable atoms of the same element we consider it "carrier-free." When stable atoms are present they are spoken of as "carrier." Some of our isotopes, like radioactive iodine, can be obtained in practically carrier-free state and others, like radioactive gold, are usually obtained diluted with a relatively large amount of the stable element. The presence or absence of this carrier may be of great clinical importance. When we make a statement about the dose of a radioisotope, this in itself implies nothing about the presence or absence of carrier, and we must usually add a qualifying statement, such as "carrier-free," or "with 5 mg. of carrier." Figure 5 attempts to illustrate this carrier. The black spots represent radioactive atoms and the open circles stable atoms. The amount of radioactivity is the same in all three samples, but the total weight of the element is thousands of times greater in the sample with considerable amounts of carrier present.

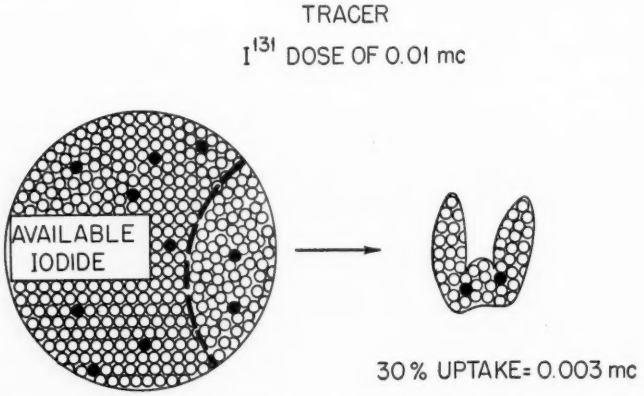


FIG. 6A. Representation of uptake of a smaller tracer dose in the thyroid.

One of the facts most difficult for us to get used to is that a tremendously large dose of radioactivity can be contained in an exceedingly small weight of a carrier-free isotope. We can have a huge dose of a radioisotope in a sample so small that if used as a stable drug it would stagger the diluting powers of the homeopath.

At this point it might be well to introduce another rather unsatisfactory term; this is "specific activity." The following definitions of this term are used:

1. The amount of radioisotope (in millicuries) per total weight of that element.
2. The amount of the radioisotope per unit weight of a chemical compound containing it.
3. The amount of the radioisotope per weight or volume of any tissue, fluid or other material.

It would be helpful if it were used only with the first meaning given, that is, the amount of the radioactive isotope per total weight of the given element. In this sense it is simply another way of expressing the amount of carrier. A sample with high carrier has low specific activity, and vice versa. The other two uses for "specific activity" are rather vague and only help to confuse the problem, but they are widespread in the literature and we must get used to them.

Radioactive iodine gives us a good illustration of the importance of carrier, or the lack of it. It is possible for us to give doses of radioactive iodine, which are very large in terms of radiation, without significantly increasing the amount of elemental iodine in the body. We might say that after a dose of radioactive iodine is given in carrier-free form, it mixes with the stable iodine already present in the body and this stable iodine serves

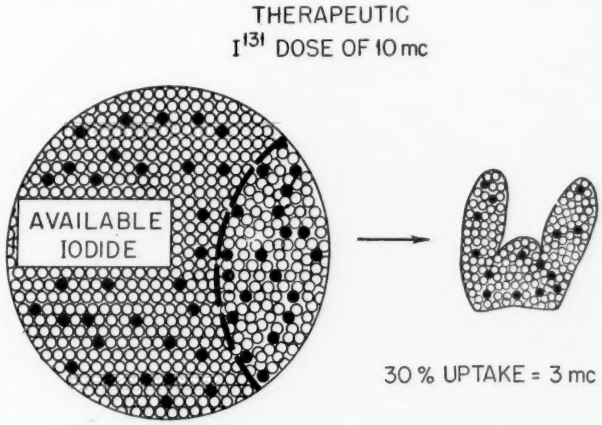


FIG. 6B. Representation of uptake of therapeutic dose of radioiodine.

as a sort of carrier. Although the amount of available iodine in the body is rather small, in terms of milligrams, it is so much larger than the doses of radioactive iodine we use that the latter have little or no diluting effect upon the total iodide pool. The next three figures illustrate this. The first figure (6A) represents a small tracer dose of radioactive iodine. The black atoms are the administered radioactive ones, and the open ones are the stable iodine already present in the body from dietary intake. We see that in this situation, in 24 hours, 30% of the available iodide goes into the thyroid, both radioactive and stable. Thus 30% of the radioactive dose will go in. In the next figure (6B) we see what happens with a much larger dose of radioactive elements. We have still not added enough iodine to swell the body pool.* The thyroid is still taking up 30% of the available

* For those who are of obsessive-compulsive personality it should be stated that the exact number of dots is not correct: there should be 1,000 times as many black ones in B as in A, and the number in B should still be minute in comparison to the total number of atoms represented.

iodide, both stable and radioactive, and 30% of our much larger dose again is taken up by the thyroid gland. Thus the percentage uptake of carrier-free iodide is essentially independent of the dose given. (Parenthetically, we might state that if a large dose is given, over a period of a few days there will be radiation changes in the gland which will alter thyroid metabolism and the rate of excretion.) If we give a really large amount of iodine, either radioactive or stable, such as might be contained in a drop or two of Lugol's solution, the iodide pool is swollen and the amount cleared by the thyroid is much less. Figure 6C illustrates this situation. When any dose of radioiodine, large or small, is given with a significant dose of carrier, the amount cleared will be greatly reduced. Conceivably, one could give enough radioactive iodine to produce this flooding effect also. However, to do this with

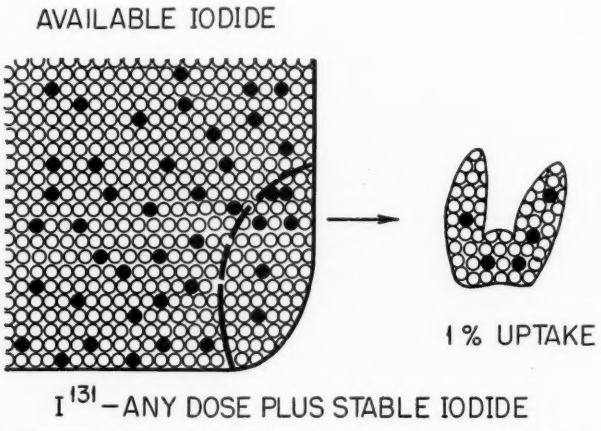


FIG. 6C. Representation of uptake of any dose diluted with added stable carrier.

carrier-free material would require so much radioiodine that the doctor and patient would both be dead from radiation before any significant measurements could be taken. Such is the potency of carrier-free radioactive iodine.

HALF-LIVES AND HALF-TIMES

Another set of terms commonly encountered in relation to radioisotopes has to do with the changing situation with the passage of time after a radioisotope is administered. We are frequently interested in considering the disintegration rate either in the whole body or in a specific organ at a given time interval after the isotope is administered. This disintegration rate is influenced by the physical half-life of the isotope, which remains the same wherever the material may be, and also by the biologic pattern of concentration and removal of the isotope, which of course varies depending upon many biologic factors. Figure 7 attempts to explain these relationships for

radioactive iodine in the normal thyroid gland. The chart begins at the point of maximal concentration of the isotope in the gland, perhaps 24 hours after it is administered. First, physical decay is shown, as always, as a straight line on semilog paper with the half-life at eight days. Second, true biologic loss represents the actual removal of iodine (whether radioactive or stable is of no consequence) from the thyroid gland. This is a rather slow process and is indicated to have a half-time of 24 days. It is not truly a straight line on semilog paper, since removal is relatively more rapid in the earlier part of the period. But for practical purposes the straight line

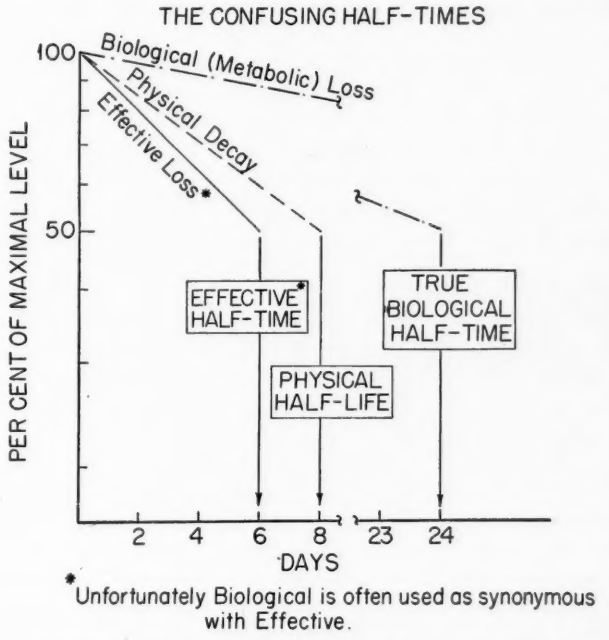


FIG. 7. Representation of the half-times for radioiodine after maximal uptake in the thyroid gland.

representation is not too far wrong. Third, we have the effective decay, which is the actual number of disintegrations occurring in the thyroid gland at various time intervals. This has gone down to 50% of maximum in six days. The effective decay is of course influenced by the true biologic loss and the physical decay. The effective decay is also not truly linear, in that it is dependent on biologic loss. The effective decay curve is what would be obtained by external counting over the gland if the actual counts were recorded uncorrected for physical decay. If they are corrected for physical decay, then these counts would show the true biologic loss. The

real complications develop because frequently the term "biological" is used to mean "effective" as the latter term is used in this chart. Therefore, when we meet the expression "biologic half-time" or "biologic decay," we do not know whether it refers to true metabolic loss or whether it is intended to be synonymous with "effective."

Distribution of Radioisotopes in Tissues

Now let us turn our attention from some of the dynamic changes in concentration of isotopes and in disintegration rates, and emphasize for a moment the anatomic location of radioactive materials in the body at any given time. Of course the position of the radioactive atoms varies depending upon the metabolic pattern and the time after administration at which the study is made. But a few general comments can be made about radioactive isotope distribution when it is looked at as a static situation at any given time. It is to be emphasized that at this particular moment we are not directly concerned with radiation dose to the tissues, or with dynamic metabolic changes, but are thinking simply of the actual position of the radioactive atoms at a given point in time. We may be interested from two different viewpoints. First, we can attempt to account for all of the retained radioisotope in the body and try to indicate the amounts in each organ or set of tissues expressed as a percentage of retained dose. On the other hand, we may be interested primarily in the relative concentrations in different tissues, or in different parts of the same tissue, without being particularly interested in the over-all partition of the dose. For example, we might be interested in knowing that 30% of a given dose of radioactive iodine was in the thyroid gland. This knowledge would not tell us the concentration in terms of microcuries in a gram of thyroid tissue unless we knew also the dose given, the size of the thyroid, and the degree of uniformity of distribution.

In a consideration of these problems it is very helpful for us to know whether any particular isotope is concentrated uniformly in the tissue of interest. Autoradiograms have been of great assistance in answering this problem. From a mass of complicated information the following generalizations can be made. Most radioactive materials that have been studied are grossly unevenly distributed in most tissues. There are only a few examples in which there appears to be a grossly uniform pattern of deposition. Examples of these are, as would be expected, tissues of rather uniform composition such as skeletal muscle, liver, spleen and thyroid. Organs made up of more than one type of tissue grossly, such as brain and bone, have nonuniform patterns of isotope distribution. Even in situations where the gross pattern appears to be quite uniform, microscopic autoradiograms show that there is a considerable unevenness of the distribution pattern.

From the autoradiographic information we can interpret studies of radioassays of tissue. We find that samples of a gram or more of one of the types of tissue giving a rather homogeneous autoradiogram are fairly accurate in predicting the over-all concentration of the isotope in the organ. On the other hand, such samples assayed from organs showing nonuniform distribution by autoradiography will be exceedingly misleading. Figure 8 shows three autoradiograms that are examples of fairly uniformly distributed radioactivity. Figure 9 indicates the more common pattern of grossly nonuniform distribution of the radioactivity. Figure 10 shows how a misleading result might be obtained if we did not have the autoradiographic information about isotope distribution. A sample of the femur is taken for

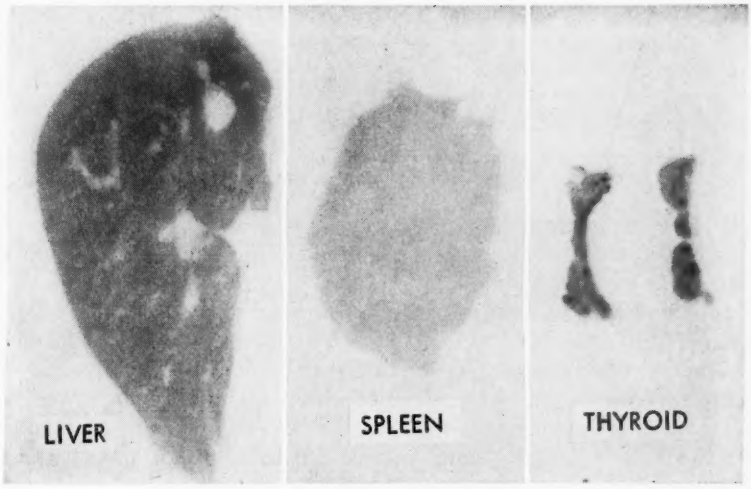


FIG. 8. Three gross autoradiograms—different tissues and different isotopes to illustrate reasonably uniform isotope distribution.

radioassay and it is found that there is 0.017 microcurie per gram. If we then estimate that the whole skeleton of the patient is 10% of the body weight, we may multiply the concentration per gram by the estimated weight of the skeleton. We thus come to the conclusion that the skeleton contains 119 millicuries of radioactive phosphorus. However, when we look at an autoradiogram of this tissue (figure 11), we discover that we had accidentally * chosen our sample from an area of unusually high concentration of the radioactivity. Assay at another point shows an entirely different value. Our over-all calculated results for the content in the skeleton is wrong by several hundred per cent. Thus we find that if we wish to express the total amount of an isotope in an organ, and thus the percentage of re-

* I really did it on purpose.

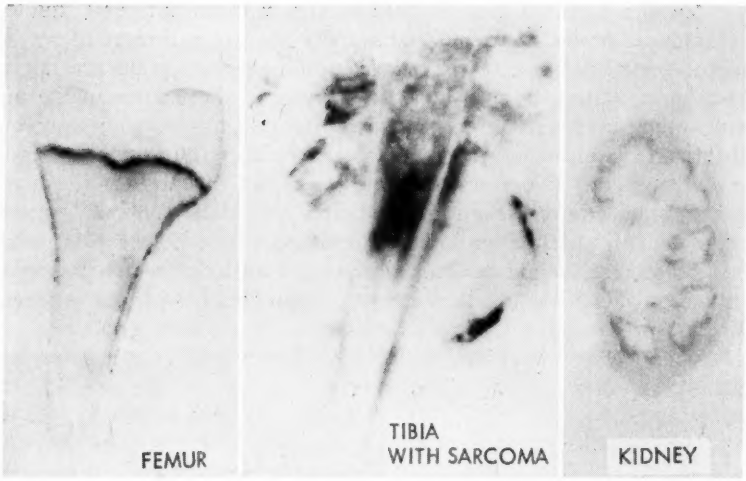


FIG. 9. Three gross autoradiograms—different isotopes and different tissues to illustrate more usual pattern of nonuniform distribution of radioactivity.

tained dose in that organ, we must assay either a very large part of the organ or a truly representative sample. Autoradiograms help us to tell how close to the truth we are coming.

In expressing concentrations of radioisotopes we sometimes use the DAR, or differential absorption ratio. This is simply a device for helping us compare concentrations of isotopes in tissues when we are dealing with groups of patients who have received different initial doses. We merely prepare a table showing the actual microcuries per gram of tissue, and then correct all the results by some type of equalizing factor to make various

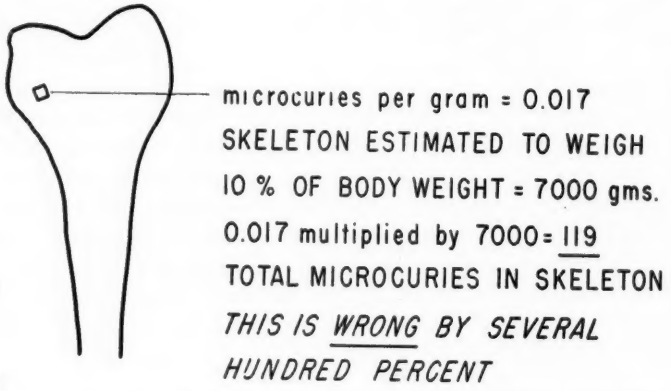

microcuries per gram = 0.017
SKELETON ESTIMATED TO WEIGH
10 % OF BODY WEIGHT = 7000 gms.
0.017 multiplied by 7000 = 119
TOTAL MICROCURIES IN SKELETON
THIS IS WRONG BY SEVERAL
HUNDRED PERCENT

FIG. 10. Example of erroneous concentration for organ content based upon a nonrepresentative sample.

patients comparable to each other. Sometimes this equalizing factor is obtained by dividing the retained dose by the patient's total weight and obtaining from this a theoretic average concentration. Then the actual measured concentrations are divided by this derived figure and the values obtained are used for study and comparison. It is obvious that a value of 1 would represent an average distribution, assuming no specific concentration or rejection of the isotope. Values higher than 1 would indicate a specific concentrating mechanism. These figures may be called the "DAR Whole Body." We also sometimes use, instead of the theoretic figure for average concentration, an actual measured figure for some organ usually chosen as not being likely to have much intrinsic variation in avidity for the radioisotope. For example, we may consider the concentration in muscle to be

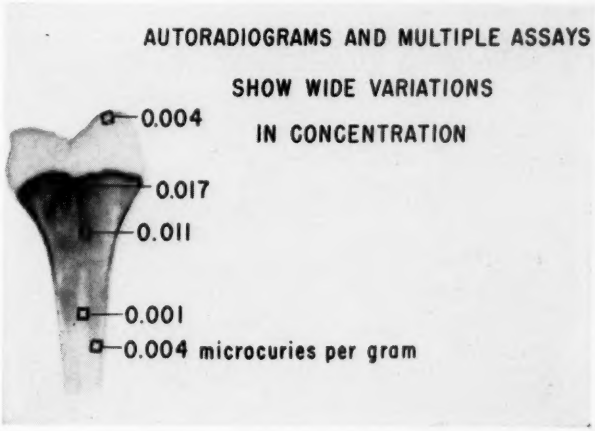


FIG. 11. Autoradiogram and selective assays in the same sample show wide range of concentration.

unity. Dividing all the other assay values by the concentration in muscle, we have an expression of concentration relative to muscle and this may be called "DAR Muscle." When we think of these isotope distribution patterns it is important to keep in mind that tissues do not all have the same density, and the concentration per gram is not necessarily directly proportional to the concentration per cubic milliliter. Bone, of course, with its high density, is the tissue in which this difference is of greatest magnitude.

. RADIATION DOSAGE TO THE TISSUES

We have so far said nothing directly about the dosage of radiation received by the tissues. Here again we get into complications of terminology. The roentgen, which was the original unit for this dosage, was defined for X or gamma radiation only, and was, by definition, expressed as a quantity

of ionization in a unit of air. A newer unit, the rad, corrects for some of the difficulties with the roentgen and tries to express the dosage in terms of energy dissipated. Without our going into these problems, a few general statements might be made about tissue dosage. First of all, we should emphasize that the dosage units have to do with the interaction of the radiations with the tissue and do not correspond, necessarily, in any simple way to the nuclear changes involved at the origin of the radiation. The curie units should be thought of in terms of the origin of the radiation, whereas the roentgen or rad has to do with the interaction with tissue at the other end of the path of radiation. The curie, as has been stressed, is a statement of disintegrations per unit time, but the rad and roentgen are in terms of total energy absorbed over an infinite time unless stated otherwise, as, for example, "roentgens per minute." When radioisotopes are used externally in teletherapy machines, the beam of gamma rays directed into the body is very similar to the beam of x-rays long familiar to radiotherapists. Differences in the energies of the gamma rays affect the dosage absorbed in the tissues, but these energy changes are quite predictable and there is no great difficulty in relating dosages from teletherapy machines to dosages administered by x-ray tubes.

On the other hand, when we deal with isotopes present *within* the body we get into great difficulties in relating the tissue dosage to our familiar concepts derived from experience with external beams. For one thing, it is clear that the distribution of the radiation does not necessarily correspond to the distribution of the radioisotope. We know that with internally administered beta emitters the radiations are limited to an area within a few millimeters of the actual site of the radioactive atom. However, with gamma emitters the radiations affect distant tissues which may not contain any of the radioisotope. Efforts to express the energy absorption in the tissues in terms of equivalent roentgens have led to many difficulties. It appears that the radioisotopes, particularly the beta emitters, are much less effective than they theoretically should be. The major explanation for this discrepancy lies in the fact that the dosage calculations for internal beta emitters are based upon an assumed uniform distribution of the isotope in the tissues. Actually, the distribution is uneven, usually grossly so and always microscopically so. This means that some cells get much more radiation than do others. Frequently there are foci of excessive radiation dose, and in these areas the cells may receive enough radiation to be killed many times over. However, they can die only once, and any additional radiation received is essentially ineffective. Thus, although our calculated dosage may suggest a generalized moderately high level, what we are really dealing with is a combination of exceedingly high doses at certain points with relatively low doses at other points. In terms of histologic effects and functions, it appears that the minimal radiation dose, rather than the maximal radiation dose, is usually of greatest significance in determining

the results. This is certainly true in the treatment of neoplasms, where total destruction is desired. In general, our isotope therapy is only as good as the poorest dosage obtained.

With the gamma emitters a somewhat more uniform dosage distribution results. In practical experience we are always dealing with some degree of beta radiation along with the gamma emissions, and it is difficult to make a clear separation. With gamma rays we cannot assume that all the radiation produced is absorbed in the body. The amount that is absorbed depends a great deal upon the position of the isotope in the body; therefore, no simple generalizations on the amount of gamma tissue dosage to be obtained from a given amount of isotope can be made.

It is important, too, to remember that with most of our experience with external therapy we are dealing with a relatively rapid dosage rate, the total number of roentgens usually being given in multiple treatments each of a few minutes' duration; with radioisotopes we are dealing with a prolonged, gradually diminishing delivery of radiation dosage. It is surprising that we do not see even more striking differences than we do see, considering the great difference in dosage rates of the two types of radiation treatment.

The preceding discussion is obviously a superficial and incomplete one, but it covers, in a general way, many of the concepts necessary for the clinical use of radioisotopes. These general principles can be understood without much knowledge of mathematics or physics.

In addition to these basic principles there are many interesting and important clinical facts having to do with the use of radioisotopes. As evidence of the importance of internists in the development of radioisotope knowledge we have in this country the distinguished contributions of such men as Blumgart, Chapman, Freedberg, Hertz, John H. Lawrence, Osgood, Rawson, Reinhard, Seidlin and others. Physicians trained in internal medicine have an unusually good background for the understanding of many clinical isotope procedures, including especially the studies relating to nutrition and electrolyte balance, as well as the study and treatment of thyroid diseases and hematologic disorders.

Acknowledgment

The author wishes to thank William D. Gibbs and Ralph M. Kniseley for help in preparing the illustrations for this presentation.

Summario in Interlingua

Radioisotopos deveni de plus in plus importante in le practica clinic. Recente progressos ha concernite principalmente le campo del studios diagnostic que reguarda le internista plus tosto que le radiologo. Certe informationes fundamental es requirite pro le execution e le interpretation de tal studios. Extense cognoscentias de physica non es indispensabile pro comprender le majoritate del technicas a isotopos, e il esserea reconfortante pro numerose medicos poter tractar le problemas del radioisotopos como

extensiones del plus familiar conceptos del pharmacologia. Le characteristica primari del radioisotopos es le facto que illos produce radiationes. Iste radiationes pote esser detegite e mesurate; illos pote lesionar cellulas vive e migrar varie distantias intra le histos. Le majoritate del studios traciatori e diagnostic se basa super le facto que, in general, atomos radioactive se comporta biochimica- e metabolicamente in le mesme maniera como le atomos stabile del mesme elemento. Es possibile presentar varie conceptos in forma simplificate, como per exemplo le conceptos de unitates de dosage, disintegration physic, efficace periodo de medie valor, e portator. Esseva facite le effortio a clarificar certe areas de confusion in re le "periodo de medie valor biologic," le intensitate de radiation vis-a-vis millicuries, e "activitate specific."

Simple graphicos e diagrammas illustra iste punctos.

"SPECIFIC" DISEASES SIMULATING "NONSPECIFIC" ULCERATIVE COLITIS (LYMPHOPATHIA VENEREUM, ACUTE VASCULITIS, SCLERODERMA AND SECONDARY AMYLOIDOSIS *

By Moshe B. Goldgraber, M.D., and Joseph B. Kirsner, M.D., F.A.C.P., *Chicago, Illinois*

Nonspecific ulcerative colitis is an acute and chronic disease of the colon, of obscure etiology and pathogenesis.[1] The diagnosis is established on the basis of clinical symptoms, typical proctoscopic and roentgenologic features, and the absence of specific pathogenic bacteria or parasites in the feces. Despite the almost characteristic features, the disease may be simulated clinically by disorders of the colon of more "specific" genesis. The study of these special problems is of unique interest, because clarification of their particular pathogenesis may shed light on the development of the "idiopathic" variety of ulcerative colitis. Four examples of "specific" diseases simulating ulcerative colitis clinically are (1) lymphopathia venereum, (2) acute vasculitis of the colon, (3) scleroderma, and (4) secondary amyloidosis.

Lymphopathia Venereum

Palmer, Kirsner and Rodaniche [2] studied a group of 10 white patients with symptoms of rectal bleeding, mucopurulent discharge from the anus, stricture formation, and inflammation of the colon. All had positive Frei tests and neutralizing antibodies in the serum. In five of the group, the virus of lymphopathia venereum was isolated directly from rectal biopsies. It was concluded that lymphopathia venereum may simulate chronic, "nonspecific" ulcerative colitis.

The possibility of a virus infection in chronic idiopathic ulcerative colitis led to skin tests with a Frei antigen in 33 cases.[3] Two of this group had a positive dermal reaction, and virus neutralizing antibodies were present in the serum; however, the virus could not be isolated from rectal tissue. These studies indicated that lymphopathia venereum and chronic ulcerative colitis are independent diseases, which may resemble each other proctoscopically and clinically.

Lymphopathia venereum may simulate regional enteritis more closely. The primary lymphatic involvement, stenosis and fistulae formation are the principal features. However, skin tests of patients with regional enteritis

* Received for publication April 10, 1957.
From the Department of Medicine, The University of Chicago.
Requests for reprints should be addressed to Moshe B. Goldgraber, M.D., Department of Medicine, The University of Chicago, Chicago 37, Illinois.

with the Frei antigen were negative.[4] The serum of these patients did not contain neutralizing antibodies for the viral antigen, and surgical specimens of diseased ileum and lymph nodes failed to reveal viral agents by the technics employed.

Case Reports

Case 1. A 40 year old white male came to the University of Chicago Clinics for the first time in November, 1933. He had been troubled by an anal fistula for nine months and severe tenesmus for six months, and had noted a mucopurulent rectal discharge, with approximately eight evacuations daily. He had contracted a penile lesion in 1926, which had been treated with intramuscular injections. He developed a similar lesion two years later; blood serologic tests for syphilis at that time were positive, and antibiotic treatment was given. Physical examination demonstrated a scar in the anal region from a fistula previously operated upon and another fistula in the process of healing. Stenosis of the rectum at the tip of a finger length was noted on digital examination. At proctoscopy, the visualized mucosa of the rectum appeared granular and friable.

In 1936 an elongated constricting lesion of the transverse colon (near the splenic flexure) was found at x-ray examination elsewhere. Six inches of the colon were resected and an end-to-end anastomosis was performed. The mucosa of the surgical specimen was studded with multiple confluent ulcers, and there was marked constriction of the intestinal lumen. The edges of the ulcers were hypertrophic and pseudopolypoid. The Frei test was negative at that time. A diagnosis was made of ulcerative colitis, Group III, to define the unknown etiology of this type of colitis and its somewhat unusual features.[5] The patient was hospitalized at the Albert Merritt Billings Hospital in December, 1937, because of repeated rectal bleeding. Roentgen examination revealed a narrowed descending and sigmoid colon. An elongated, constricted area was present in the midportion of the transverse colon, and the adjacent transverse colon on the right had a honeycomb appearance on the evacuation films. The Frei test was positive. A colostomy was performed in the right colon, and at that time an inflammatory mass was noted in the midtransverse colon. The patient improved and gained weight, but required rehospitalization because of swelling of the knee. He received sulfanilamide, 6 gm. daily for one week. Subsequently he had a positive Frei test; the serum contained neutralizing antibodies against lymphogranuloma virus; however, a rectal biopsy failed to demonstrate the virus. The colostomy was revised in June, 1951. In 1955, the patient recovered from a myocardial infarction.

No surgical pathologic material from this case was available for review.

Comment: The clinical picture in this case simulated ulcerative colitis so closely that it was diagnosed as such. However, the positive Frei reaction, positive serum neutralization test and the somewhat unusual distribution and appearance of the lesions were clearly compatible with lymphopathia venereum, despite failure to isolate the virus.

Acute Vasculitis

Vascular changes in the colon have long been recognized as responsible for a clinical and pathologic picture resembling ulcerative colitis. Hale-White[6] in his classic paper included two such instances. One patient had extensive atheroma of all major and minor arteries; the other, thrombosis

of the aorta and the superior mesenteric artery. Both had inflamed and ulcerated colons, with generalized or localized peritonitis. The author stressed the shortness of the symptomatic period as the only difference from "simple ulcerative colitis." Martin [7] reported a case of ulcerative colitis with death from thrombosis of the aorta with embolization. Wold and Baggenstoss [8] studied the gastrointestinal lesions of periarteritis nodosa in 30 cases; 76% had symptoms referable to the gastrointestinal tract; 70% had lesions in this system consisting of hemorrhages and infarcts. This study is of interest because of the findings of segmental involvement of vessels, exclusive involvement of vessels of one determined size, partial involvement of the vascular wall, etc. In a study of 60 cases of mesenteric vascular occlusion, Johnson and Baggenstoss [9] found three cases of periarteritis nodosa with ulcerations, secondary perforations and peritonitis, and one instance of ulcerative colitis. The occlusion of the mesenteric artery in this case was caused by arteritis and thrombosis. Warren and Sommers [10] observed 19 patients (of 180) with lesions designated as vasculitis or type A ulcerative colitis; 12 of the 19 in this group were studied at autopsy. The authors noted no significant fluctuation in the age incidence, so characteristic of chronic idiopathic ulcerative colitis. The principal pathologic feature was inflammation around medium-sized submucosal arterioles. The appearance of the lesions suggested periarteritis nodosa or thromboangiitis obliterans. Karsner [11] mentions a case of polyarteritis nodosa involving the mesenteric arteries, with multiple infarcts of the intestines; death resulted from peritonitis. Jernstrom and Stasney [12] described a Negro female, 52 years of age, who died after a short illness characterized by epigastric pain, arthralgia, abdominal tenderness and distention. At necropsy, superficial ulcers were found in the ileum and throughout the colon. Small arteries of the gastric and intestinal walls had all four stages of polyarteritis, as described by Arkin.[13] MacMahon et al.[14] described the case of an acutely ill male who, at necropsy, presented the appearance of acute panarteritis, with involvement of the vessels of the duodenal wall. Relman et al.[15] reported a patient with an acute necrotizing inflammation of small and medium sized arterioles in the esophagus, ileum, colon and gall-bladder.

In the material examined thus far we had not encountered vasculitis, nor had Lumb [16] in his study of acute cases. The following report, therefore, is of particular interest.

Case 2. A 34 year old white female had had hay fever for approximately 15 years. She was admitted to another hospital for delivery at the end of an uneventful, full term pregnancy. While in the hospital she developed an upper respiratory infection with bronchopneumonia. A cesarean section was performed because of protracted labor. Three days later, signs of intestinal obstruction developed, with rectal bleeding. Sigmoidoscopy at that time apparently did not reveal any abnormalities. The patient was explored surgically and the cecum and ascending and transverse colon were noted to be markedly distended; a segment of bowel near the splenic flexure was thickened and congested; the adjacent mesenteric nodes were enlarged.

A cecostomy was performed. Two days later a renal shut-down ensued, with only 60 c.c. of urine produced in 40 hours; the urine contained albumin, red blood cells and granular casts. The blood pressure increased and convulsions developed. The administration of cortisone, 100 mg., led to improvement of symptoms for five days. Bloody diarrhea developed subsequently, together with a bloody discharge from the

FIG. 1. *Case 2.* Vascular lesions in the submucosa and hemorrhagic infarction of the mucosa. × 250.

cecostomy. An emergency operation became necessary and a subtotal colectomy was performed; the colon was resected from the midtransverse to the midsigmoid region, with a colostomy in the left lower quadrant. Multiple transfusions were necessary postoperatively. Three days after operation oliguria ensued again, with the same microscopic findings. The blood pressure was 176/100 mm. of Hg, and the patient developed jaundice. The serum bilirubin was 5 mg.%. Convulsions reappeared and

responded to Veriloid. Two weeks after operation a suprapubic abscess was incised. The patient later improved greatly.

Histologic examination of the resected specimen demonstrated striking vascular lesions in the medium and small sized arteries of the submucosa (figure 1). There was fibrinoid necrosis of the media, with a deposit of purplish staining hyaline substance and a marked perivascular infiltration, mostly by mononuclear cells. The

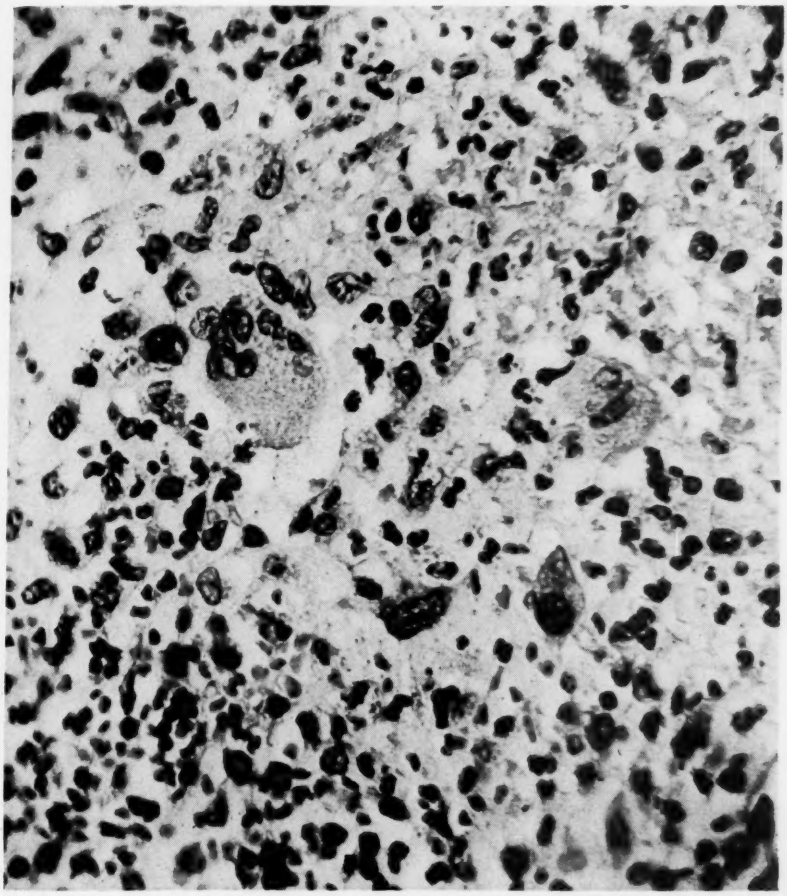


FIG. 2. *Case 2.* Granulomata and giant cells in the ulcerated mucosa. × 500.

mucosa was infiltrated with chronic inflammatory elements and engorged vessels, and presented granulomata with giant cell formation (figure 2). There was occasional marked hemorrhagic infarction. Another outstanding feature was the presence of necrotic areas with ulceration of the mucosa, unlike those seen in ulcerative colitis (figure 3).

Proctoscopy recently demonstrated a practically normal mucosa, with occasional small areas of friability. This patient has resumed an essentially normal life.

FIG. 3. *Case 2.* Mucosal ulceration. The necrotic aspect of the lesion is obvious. × 65.

Comment: This patient, with a personal and family history of allergy, became acutely ill a few days after delivery by cesarean section, with severe bloody diarrhea subsequently demonstrated to be due to an acute vasculitis of the colon. The renal symptoms suggest that the kidneys probably were involved similarly. The clinical course is strongly suggestive of a severe immunologic response to some allergen, perhaps related to a generalized Shwartzman reaction, as in an experimental animal infected with group A hemolytic streptococci and then injected with a gram-negative toxin.[17] The history of an upper respiratory infection with bronchopneumonia increases the attractiveness of the analogy. Pregnancy might facilitate the production of this reaction. A similar condition was produced in pregnant rabbits by Apitz in 1934 and by Shwartzman in 1938 with one injection only, suggesting that pregnancy increases the possibility of this type of reaction. Similar vascular changes developed in rabbits with serum sickness.[18] This case could therefore be interpreted as ulcerative colitis secondary to an acute vasculitis on a hypersensitivity basis.

Scleroderma

Systemic scleroderma is a collagen disease of unknown etiology in which acellular collagen deposited in the dermis hardens the skin. Other systems may be involved, such as joints, heart, gastrointestinal tract, kidneys, lungs, and practically every organ in the body containing connective tissue. The skin manifestations are of such prevailing importance that the disease first came to the attention of the dermatologists.[19] A small percentage of cases nevertheless start with symptoms referable to an internal organ or tissue prior to the appearance of cutaneous manifestations. The course of the disease is progressive, and in the final stages the gastrointestinal tract is involved in more than half the cases.[20] Ehrmann [21] in 1903 described a case of scleroderma with dysphagia and reported the endoscopic findings. Since then, much has been written about the esophageal complications of scleroderma.[22-37] The stomach is affected in a much smaller percentage of cases.[22, 29, 32, 34, 35] The small intestine has been involved in many cases, the main feature being dilatation of the distal portion of the duodenum and of isolated loops of the jejunum.[25, 26, 29, 35, 36, 37] In those cases where pathologic material was available,[25, 29, 31, 36, 39] the mucosa of the small bowel was infiltrated by small inflammatory elements. The submucosa contained deposits of dense collagen fibers and the muscularis was atrophic. The colon seems to be involved in a small percentage of cases, but the information in the literature is quite limited.

Scleroderma of the colon has been described repeatedly but it is a rather unusual complication. Most cases had been troubled with constipation. At x-ray, sacculation was thought to be the main feature,[25, 26, 29, 40, 41] with narrowed intervening areas. Pathologically, the dilated areas demonstrated atrophy of the muscular layer. The association of diarrhea with scleroderma

was noted in a few cases.[25, 26, 40, 41] Leinwand [37] admits that the x-ray picture may sometimes be suggestive of ulcerative colitis, but sigmoidoscopy is usually negative. Cullinan [41] believes that there is a specific sigmoidoscopic appearance of the scleroderma rectosigmoid, consisting of a gray, rigid wall, as noted in five of 11 cases.

Case 3. Scleroderma and Ulcerative Colitis. A white female, born in 1931, had experienced bouts of abdominal cramps without diarrhea at the age of five. She developed weakness, weight loss and exophthalmos at the age of 13. X-ray irradiation was directed to the thyroid, with apparent improvement. At the age of 17 she developed backache, abdominal cramps and diarrhea, with occasional bleeding; a diagnosis of ulcerative colitis was made. At that time she also experienced blanching of the skin of the fingers, mostly while exposed to cold. She developed muscle pains and stiffness of joints which became progressively worse. She had some difficulty in swallowing.

The patient was admitted to the Albert Merritt Billings Hospital in April, 1951. At that time four to five stools were passed daily, containing 4 plus occult blood. Erythematous nodular lesions were noted on the tendons and phalangeal joints of both hands; the skin over the knees was warm. Proctoscopy revealed a moderately friable, bleeding mucosa. The colon, at x-ray examination, appeared straightened, with lack of haustration, compatible with ulcerative colitis involving the entire colon. X-rays of the chest demonstrated fine nodularity, distributed over both lung fields, initially thought to represent congestive heart failure and subsequently interpreted as reflecting a diffuse collagen disease. The course was characterized by bouts of fever, and clinical signs and symptoms of pneumonitis and pericarditis. The response to ACTH was poor, to cortisone more favorable. After discharge from the hospital the patient experienced intermittent bouts of fever, joint swelling and diarrhea; arthralgia and myalgia were the major complaints. She was rehospitalized in February, 1953, at which time she had a "moon" face, fine râles at the lung bases, and swelling and tenderness of the ankles and knees, with limitations of the movement in the shoulders, wrists and fingers. The patient was sensitive to sulfaguanidine, ACTH and phenylbutazone, and required aspirin in amounts up to 10 gm. daily. A barium enema demonstrated a shortened, rigid colon without haustration, compatible with ulcerative colitis. In November, 1953, the patient underwent an emergency operation because of intractable hemorrhage from a duodenal ulcer; a subtotal gastrectomy was performed. During the subsequent five months, joint pains were especially troublesome; compound F failed to provide consistent relief. She developed an upper respiratory infection and expectorated large amounts of white mucus; a left pleural effusion was noted at fluoroscopy. A compression fracture involved T12. The patient later received 30 mc. of I^{131} in an effort to retard the progress of the scleroderma. She fell and fractured the neck of the left humerus. She was admitted for the last time in 1955 with four to five watery stools daily, persistent cough and poor appetite. Numerous transfusions were necessary. Osteoporosis was pronounced. The patient died five days after admission.

At autopsy (Dr. B. H. Spargo), the skin was thickened, atrophic and shiny over the chest and upper abdomen. The axillary hair was absent and the pubic hair sparse. There was swelling of the right elbow, with limitation of movement, and enlargement of the knee joints. The small bowel appeared normal in diameter and distribution. The colon was somewhat narrowed but approximately normal in length. The esophagus was 3 cm. in circumference and had a uniformly thickened wall with superficial ulcerations at the lower third. There was diffuse fibrosis of the lungs, with dilated bronchi. More detailed examination of the colon revealed a narrowed lumen,

with the circumference 4 cm. at the cecum and 3 cm. at the sigmoid. The mucosa of the colon was conspicuously pale and thickened.

Histologic examination revealed scleroderma of the skin, with flattening of the epidermis and deposition of acellular collagen in the dermis. There was diffuse fibrosis of the lungs, with proliferation of alveoli and small sized bronchi. In the lower esophagus there were thickening of the mucosa, hypertrophy of the muscularis mucosae and pronounced inflammatory infiltration of the lamina propria and the submucosa. The external muscle layer was largely replaced by fibrous tissue. Cellular infiltration was apparent in the lamina propria of the small bowel. The muscle layers were thinner than usual, and the muscle fibers had different tinctorial properties, an observation difficult to interpret. The mucosa of the colon manifested increased cellularity. Some sites appeared superficially ulcerated; others had a cuboid type of epithelium, often present at sites of regeneration. The muscularis mucosae was hypertrophic and the submucosa wide, with a pronounced fatty infiltration, as noted in chronic ulcerative colitis. In some restricted areas there were deposits of collagen. The arterioles had thickened walls, with proliferated intima and narrowing of the lumen. In one segment the external layer of the muscularis had a fibrotic area, as might be found with an old infarction. The serosa was diffusely thickened.

Comment: This case of scleroderma was characterized by spectacular involvement of the skin, lungs and lower esophagus. In the colon there were narrowing of the lumen, increased thickness of the wall, diffusely infiltrated mucosa, and thickened fatty submucosa. All these are evidence of chronic ulcerative colitis. On the other hand, the limited deposits of collagen in the submucosa, rather pronounced fibrosis of vessels, fibrotic area in the muscularis and thickening of the serosa are all compatible with scleroderma. The possibility of additional changes of scleroderma in a case of chronic ulcerative colitis is suggested; both scleroderma and ulcerative colitis may have coexisted.

Secondary Amyloidosis

Gastrointestinal symptoms occur quite frequently in Hodgkin's disease, but demonstrable lesions of the gastrointestinal tract are quite rare. Jackson and Parker [42] found gastrointestinal symptoms in 24 of 213 patients affected by this disease; only nine of these patients had lesions in the stomach or bowel. The primary site of the disease in six, however, was the gastrointestinal tract. The appearance of gastrointestinal symptoms is considered a poor prognostic sign in Hodgkin's disease.[43] According to Portmann et al.,[44] the colon is the least frequent site of lesions in Hodgkin's disease, and not more than eight cases could be collected by these authors from the literature. Occasionally, amyloid infiltration will complicate Hodgkin's disease,[45, 46] as it did in the present case.

The gastrointestinal involvement in amyloidosis was well known to Virchow.[47] Lubarsch [48] considered it fourth in frequency after the spleen, kidneys and adrenals. Wang and Robbins [49] described a case of "primary amyloidosis" of the colon, with widening and thickening of folds at barium enema; at necropsy, sizable areas of hemorrhages were found. The colon may be involved in amyloidosis in the same degree as is the small bowel,

but it is less frequently responsible for symptoms.[50] Dahlin [51] found a higher incidence of amyloid deposit in surgical specimens than in autopsy material, denoting, perhaps, reabsorption of the deposited substance. The reversibility of amyloid infiltrations was assumed on a clinical basis by Conheim and proved by Maximow.[52] Amyloidosis complicating ulcerative colitis and regional enteritis has been noted recently by us,[53] but the gastrointestinal symptoms could not be distinguished from those of the underlying disease. The following case of Hodgkin's disease presented symptoms interpreted as compatible with the diagnosis of ulcerative colitis; for this reason it is included in the present series.

Case 4. A Negro male, 25 years of age, was first admitted to Albert Merritt Billings Hospital in August, 1953. His illness had begun in 1946 with a generalized lymphadenopathy, and a diagnosis of Hodgkin's disease was made elsewhere. He received x-ray treatment at that time, and a year later, two courses of N_2H. He lost weight, felt weak, and had fever, anorexia and low back pain. The platelets were low and cortisone was prescribed. For the past two months the patient had diarrhea.

At physical examination a group of enlarged nodes, 2 cm. × 2 cm., was palpated in the right cervical area; small nodes were present in the right supraclavicular area, and other nodes were palpated in the left axilla, right inguinal area and left popliteal space. The abdomen was normal. Laboratory examinations revealed: hemoglobin, 8.3 gm. %; red blood cells, 2.71 million; white blood cells, 7100, platelets, 210,000. Stools were formed and were 2 plus positive to benzidine. The plasma proteins were 7.5 gm. %; albumin, 2 gm. %; globulin, 5.5 gm. %. Chest x-rays gave evidence of bilateral hilar adenopathy and a mass in the superior mediastinum on the left, interpreted as compatible with Hodgkin's disease. Sternal puncture smears and sections of needle biopsy revealed a hyperplastic marrow with increased iron storage. Lymph node biopsy was interpreted as typical for active Hodgkin's disease. Additional studies included bromsulfalein retention of 28%. The urea clearance test was 70%. Eosinophils were 331/cu. mm. The patient received N_2H, with some improvement and diminution in size of nodes. He felt better, gained weight and worked part-time. Subsequently he developed watery diarrhea, with bowel movements four to five times daily. There were increased borborygmus and gaseous distention. The temperature was 38.4° C. Stool cultures were negative. The patient was re-admitted six weeks after his discharge because of diarrhea, chills, fever, weakness and weight loss. The stools were persistently 3 to 4 plus benzidine-positive. At proctoscopy the mucosa was covered with a grayish exudate, and petechial areas of hemorrhage were noted. A polyp 1.5 by 0.8 by 0.8 cm. at a level 17 cm. above the anal ring was removed, and a biopsy from the rectal wall was taken. Proctoscopy was repeated on two additional occasions, each time with findings interpreted as ulcerative colitis.

The polyp was an adenoma, possibly malignant, and the biopsy showed inflammation, engorgement of vessels, and hyperplastic and edematous mucosa. The upper layer of the lamina propria contained small amounts of eosinophilic material (figure 4).

The patient continued to pass five to eight watery bowel movements per day. Treatment with diet, sulfaguanidine and up to 300 mg. of cortisone daily had no beneficial effect. He developed a troublesome hiccup and died after six weeks of hospitalization.

At autopsy the diagnosis of Hodgkin's disease involving the spleen, lymph nodes and lungs was confirmed, and secondary amyloidosis involving the bowel, liver, kidneys and adrenals was found. No lesions were apparent grossly in the stomach, duodenum or jejunum. The mucosa of the distal ileum contained pale, poorly circum-

FIG. 4. *Case 4.* Rectal biopsy. Cellular infiltration of the lamina propria and small deposits of amyloid below the surface between the crypts. × 165.

FIG. 5. *Case 4.* Cecal mucosa. Breaking away of the amyloid source of ulceration. × 110.

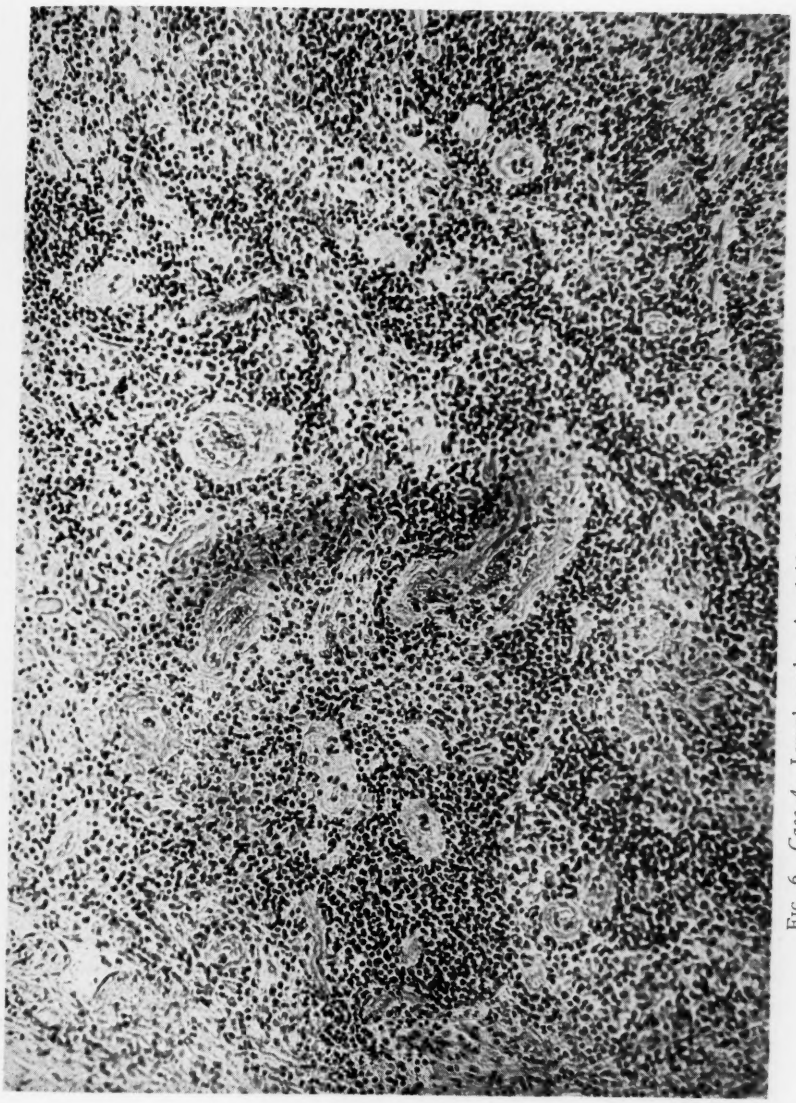


FIG. 6. *Case 4.* Lymph node. Amyloid deposits in the arteriolar wall. × 160.

scribed grayish plaques resembling ulcerative lesions. Similar plaques were seen on the mucosa of the cecum and ascending colon. In the cecum there was also a sessile polyp, 4 mm. in diameter, with a reddish granular surface. Microscopically there were deposits of amyloid (Congo red-positive) in the lamina propria of the bowel, on both the ileal and the cecal sides of the ileocecal valve. Breaking away of the amyloid in a few areas gave the picture of shallow ulcerations (figure 5). There was ulceration of the ascending colon, with edema of the submucosa and cellular infiltration. Amyloid deposition was noted in the midzones of the lobules in the liver between the cords and sinusoids. Similar deposits were seen abundantly in the glomeruli, in small arterioles of the kidneys, in subendothelial regions of capillaries in the adrenals, and in the arterioles of the lymph nodes (figure 6).

Comment: Deposit of amyloid in the intestinal wall apparently created conditions similar to those of chronic ulcerative colitis. Virchow described the fragile nature of amyloid, and this seems to be the mechanism of colonic ulcerations. Other factors probably are focal necrosis caused by vascular occlusion, as indicated by Hueter (cited in 4), and inflammatory infiltration as seen in the biopsy.

Discussion

Chronic "nonspecific" ulcerative colitis clinically resembles numerous infections of the colon, including tuberculosis,[54] bacillary dysentery [55] and amebiasis.[56] Discovery of these specific agents excludes the idiopathic variety of ulcerative colitis.[57] The search for a single, specific factor responsible for this disease has thus far been unsuccessful.[58-60] Clinical patterns identical with chronic ulcerative colitis have been encountered also in relation to fungal infections [61] and to the administration of antibiotics.[62] The casual finding of agents in the bowel content and even in the blood stream [63] does not necessarily signify their etiologic relationship to the changes in the bowel wall. The concept has been advanced [64] that ulcerative colitis originates in early childhood, although clinically the disease may not become evident until adult life. It may well be that ulcerative colitis is merely a nonspecific reaction of the bowel to injury of various types, a common denominator in many diseases of the bowel, known and unknown. This concept might explain the unproductive search for an etiologic agent, and the multiplicity of etiologic factors. These irritants may be of various nature: infections, alimentary deficiencies, toxic agents, metabolic disorders, and trauma of psychic origin. The factors determining susceptibility of the colon to psychic trauma similarly remain obscure. "Hyper-reactiveness" of the colon, perhaps on the basis of a fundamental hypersensitivity response, may be involved, though evidence in support of this attractive concept is not yet available.[65]

Summary and Conclusions

Four patients, with lymphopathia venereum, acute vasculitis, scleroderma and secondary amyloidosis, respectively, presented clinical features of "nonspecific" ulcerative colitis. The concept is advanced that the colon may

react in a nonspecific but characteristic manner to a variety of etiologic agents, resulting in "nonspecific" ulcerative colitis.

ACKNOWLEDGMENT

We are grateful to Dr. V. Wilner, of New York, for permission to use some clinical data and slides in case 2.

SUMMARIO IN INTERLINGUA

Es describite casos individual de lymphopathia veneree, vasculitis acute, e amyloidosis que simulava fortemente le syndrome clinic de chronic colitis ulcerative. In un quarte caso, le symptomas de chronic colitis ulcerative co-existeva con illos de scleroderma. Es formulate le these que le colon reage in certe casos in un nonspecific sed characteristic maniera que simula colitis ulcerative. In le varietate de colitis ulcerative que es designate como "nonspecific," il existe possibilemente un stato de hypersensibilitate in le pariete intestinal qu reage a varie stimulos per simile syndromes clinic. Le natura de iste responsa de hypersensibilitate require un clarification additional.

BIBLIOGRAPHY

1. Kirsner, J. B., and Palmer, W. L.: Ulcerative colitis. Considerations of its etiology and treatment, J. A. M. A. **155**: 341, 1954.
2. Palmer, W. L., Kirsner, J. B., and Rodaniche, E. C.: Studies on lymphogranuloma venereum infection of the rectum, J. A. M. A. **118**: 517, 1942.
3. Rodaniche, E. C., Kirsner, J. B., and Palmer, W. L.: Lymphogranuloma venereum in relation to chronic ulcerative colitis, J. A. M. A. **115**: 515, 1940.
4. Rodaniche, E. C., Kirsner, J. B., and Palmer, W. L.: Lymphogranuloma venereum and regional enteritis, Gastroenterology **1**: 687, 1943.
5. Bargen, J. A.: The modern management of colitis, 1943, Charles C Thomas, Springfield, pp. 192–202.
6. Hale-White, W.: On simple ulcerative colitis and other rare intestinal diseases, Guy's Hosp. Rep. **45**: 131, 1888.
7. Martin, M. E.: Arterial thrombosis associated with chronic ulcerative colitis, Am. J. Digest. Dis. **12**: 85, 1945.
8. Wold, L. E., and Baggenstoss, A. H.: Gastro-intestinal lesions of periarteritis nodosa, Proc. Staff Meet., Mayo Clin. **24**: 28, 1949.
9. Johnson, C. C., and Baggenstoss, A. H.: Mesenteric vascular occlusion. II. Study of 60 cases of occlusion of arteries and of 12 cases of occlusion of both arteries and veins, Proc. Staff Meet., Mayo Clin. **24**: 649, 1949.
10. Warren, S., and Sommers, S. C.: Pathogenesis of ulcerative colitis, Am. J. Path. **25**: 657, 1949.
11. Karsner, H. T.: Acute inflammations of arteries, 1947, Charles C Thomas, Springfield, p. 30.
12. Jernstrom, P., and Stasney, J.: Acute ulcerative enteritis due to polyarteritis, J. A. M. A. **148**: 544, 1952.
13. Arkin, A.: A clinical and pathological study of periarteritis nodosa, Am. J. Path. **6**: 401, 1930.
14. MacMahon, H. E., Derow, H. A., and Patterson, J. F.: A variant of periarteritis nodosa, Bull. New England M. Center **15**: 161, 1953.
15. Relman, A. S., MacMahon, H. E., and Patterson, J. F.: Vasculitis involving the gastrointestinal tract, lungs and kidneys, Bull. Tufts New England M. Center **2**: 48, 1956.
16. Lumb, G., Protheroe, R. H. B., and Ramsay, G. S.: Ulcerative colitis with dilatation of the colon, Brit. J. Surg. **93**: 182, 1955.

17. Thomas, L.: The generalized Shwartzman reaction on rabbits injected with group A hemolytic streptococci, *in* Rheumatic fever, a symposium held at the University of Minnesota in 1951, 1952, University of Minnesota Press, Minneapolis, pp. 232–246.
18. Hopps, H. C., and Wissler, R. W.: The experimental production of generalized arteritis and periarteritis (periarteritis nodosa), J. Lab. and Clin. Med. **31**: 939, 1946.
19. Rothman, S., and Malkinson, F. D.: Changes in the gastrointestinal tract in scleroderma and other diffuse connective tissue diseases, presented at the Second Annual Convention of the American College of Gastroenterology at the Shoreland Hotel, Chicago, October 27–29, 1955.
20. Piper, W. N., and Helvig, E. B.: Progressive systemic scleroderma, Arch. Dermat. **72**: 535, 1955.
21. Ehrmann, S.: Ueber die Beziehung der Sklerodermie zu den autotoxischen Erythemen, Wien. med. Wchnschr. **53**: 1097, 1156, 1903.
22. Rake, G.: On the pathology and pathogenesis of scleroderma, Bull. Johns Hopkins Hosp. **48**: 212, 1931.
23. Weiss, S., Stead, E. A., Warren, J. V., and Bailey, O. T.: Scleroderma heart disease, with a consideration of other visceral manifestations of scleroderma, Arch. Int. Med. **71**: 749, 1943.
24. Lindsay, J. R., Templeton, F. E. L., and Rothman, S.: Lesions of the esophagus in generalized progressive scleroderma, J. A. M. A. **123**: 745, 1943.
25. Hale, C. H., and Schatzki, R.: The roentgenological appearance of the gastrointestinal tract in scleroderma, Am. J. Roentgenol. **51**: 407, 1944.
26. Goetz, R. H.: The pathology of progressive systemic sclerosis (generalized scleroderma), Clin. Proc. **4**: 337, 1945.
27. Olsen, A. M., O'Leary, P. A., and Kirklin, B. R.: Esophageal lesions associated with acrosclerosis and scleroderma, Arch. Int. Med. **76**: 189, 1945.
28. Pugh, D. G., Kvale, W. F., and Margulies, H.: Scleroderma with involvement of the viscera: report of a case, Proc. Staff Meet., Mayo Clin. **20**: 410, 1945.
29. Bevans, M.: Pathology of scleroderma with special reference to the changes in the gastrointestinal tract, Am. J. Path. **21**: 25, 1945.
30. Rafsky, H. A., and Herzig, W.: Scleroderma with esophageal symptoms: report of 2 cases, Gastroenterology **7**: 35, 1946.
31. Lushbaugh, C. C., Rubin, L., and Rothman, S.: Scleroderma of the intestinal tract: first report of a fatal case, Gastroenterology **11**: 382, 1948.
32. Kaisch, A. M.: Clinical and roentgenological aspects of esophageal lesions in scleroderma, Am. J. Digest. Dis. **16**: 405, 1949.
33. Schwartz, G. S., and Skisness, O. K.: Generalized progressive scleroderma, Am. J. Roentgenol. **62**: 359, 1949.
34. Aronson, S. M., and Wallterstein, L.: Protean nature of scleroderma with a note on pulmonary changes, New York State J. Med. **50**: 2723, 1950.
35. Boyd, J. A., Patrick, S. F., and Reeves, R. J.: Roentgen changes observed in generalized scleroderma. Report of 63 cases, Arch. Int. Med. **94**: 248, 1954.
36. Abrams, H. L., Carnes, W. H., and Eaton, J.: Alimentary tract in disseminated scleroderma with emphasis on small bowel, Arch. Int. Med. **94**: 61, 1954.
37. Leinwand, F., Duryee, W. A., and Richter, M. N.: Scleroderma (based on a study of over 150 cases), Ann. Int. Med. **41**: 1003, 1954.
38. Papel, W., and Treip, C. J.: Viscero cutaneous collagenosis. A study of the intermediate forms of dermatomyositis, scleroderma and disseminated lupus erythematosus, J. Clin. Path. **8**: 1, 1955.
39. Marshall, F.: Collagen disease of the small bowel, New England J. Med. **255**: 978, 1956.
40. Kemp-Harper, R. A.: The radiological manifestations of diffuse systemic scleroderma, Proc. Roy. Soc. Med. **46**: 512, 1953.
41. Cullinan, E. R.: Scleroderma, Proc. Roy. Soc. Med. **46**: 507, 1953.

42. Jackson, H., Jr., and Parker, F., Jr.: Hodgkin's disease and allied disorders, 1947, Oxford University Press, New York.
43. Dagradi, A. E., Reingold, J. M., and Borreson, R. E.: Primary Hodgkin's disease of the stomach. A case report with a note on pathogenesis, Gastroenterology **30**: 824, 1956.
44. Portmann, U. V., Dunne, E. F., and Hazard, J. B.: Manifestations of Hodgkin's disease of the gastrointestinal tract, Am. J. Roentgenol. **72**: 772, 1954.
45. Randall, C. S.: Multiple myeloma complicated by intestinal obstruction due to amyloid infiltration of the small intestine, Am. J. Cancer **19**: 838, 1933.
46. Dahlin, D. C.: Amyloidosis, Proc. Staff Meet., Mayo Clin. **24**: 637, 1949.
47. Virchow, R.: Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre, 1859, August Hirschwald, Berlin, pp. 334, 349.
48. Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Bd. 4, Heft 3, 1929, Julius Springer, Berlin, p. 55.
49. Wang, C. C., and Robbins, L. L.: Amyloid disease. Its roentgen manifestations, Radiology **66**: 489, 1956.
50. Korelitz, B. J., and Spindell, L. N.: Gastrointestinal amyloidosis. Report of case and review of clinical and radiological aspects, J. Mt. Sinai Hosp. **23**: 683, 1956.
51. Dahlin, D. C., and Dockerty, M. B.: Amyloid and myeloma, Am. J. Path. **26**: 581, 1950.
52. Humphreys, E. M.: Personal communication.
53. Albert Merritt Billings Hospital Cases #528319 and #643480.
54. Kogan, E., and Janovitz, H. D.: Intestinal tuberculosis: difficulties in diagnosis in absence of florid pulmonary involvement, J. Mt. Sinai Hosp. **23**: 597, 1956.
55. Felsen, J., and Garenberg, H.: Chronic dysentery, distal ileitis and ulcerative colitis. A follow-up of the Jersey City epidemic of bacillary dysentery, Am. J. M. Sc. **192**: 553, 1936.
56. Craig, C. F.: Etiology, diagnosis and treatment of amebiasis, 1944, the Williams and Wilkins Company, Baltimore, p. 99.
57. Buie, L. A.: Chronic ulcerative colitis, J. A. M. A. **87**: 1271, 1926.
58. Buie, L. A., and Bargen, J. A.: Chronic ulcerative colitis: a disease of systemic origin, J. A. M. A. **101**: 1463, 1933.
59. Kirshen, M.: Ulcerative colitis: an evaluation of the etiology, symptomatology and therapy, Am. J. Digest. Dis. **14**: 384, 1949.
60. Ginsberg, R. S., and Ivy, A. C.: The etiology of ulcerative colitis: an analytical review of the literature, Gastroenterology **7**: 67, 1946.
61. Henderson, R. G., Princerton, H., and Moore, L. T.: *Histoplasma capsulatum* as a cause of chronic ulcerative colitis, J. A. M. A. **118**: 885, 1942.
62. Klotz, A. P., Palmer, W. L., and Kirsner, J. B.: Aureomycin proctitis and colitis: a report of five cases, Gastroenterology **25**: 44, 1953.
63. Moolten, J. E., Clark, E., Glasser, B. F., Katz, E., and Miller, B. S.: Blood stream invasion by Newcastle disease virus associated with hemolytic anemia and encephalopathy, Am. J. Med. **14**: 294, 1953.
64. Portis, S. A.: Idiopathic ulcerative colitis, J. A. M. A. **139**: 208, 1949.
65. Kirsner, J. B.: Ulcerative colitis: observations on its etiology, course and treatment, Postgrad. Med. **22**: 132, 1957.

EVIDENCES FOR CLINICAL MAGNESIUM DEFICIENCY *

By Edmund B. Flink, M.D., F.A.C.P., Robert McCollister, M.D., Ananda S. Prasad, M.D., James C. Melby, M.D., and Richard P. Doe, M.D., *Minneapolis, Minnesota*

We shall attempt to present evidence that magnesium deficiency is a clinical problem, that it presents distinctive clinical features, and that it is not uncommon. A brief review of some of the facts about magnesium will be made and then evidence from the clinical course of patients, balance studies and correlation of findings will be presented.

An adult human body weighing 70 kg. contains about 21.0 gm. of magnesium, according to Shohl,[1] and about 29 gm., according to Widdowson, McCance and Spray [2] and Duckworth and Warnock.[3] This discrepancy can be accounted for chiefly by differences in the skeletal content. Calculations of the soft tissue content of magnesium, using intracellular and extracellular fluid volumes [4] and concentrations from data in the literature,[5] indicate that not more than 10.0 gm. are found in soft tissues, and less than this amount is likely. Duckworth and Warnock [3] cite data that the soft tissue content has been variably estimated to be 7.2, 7.3, 8.2 and 10.0 gm. for a 70 kg. person. An approximation of the magnesium distribution in a 70 kg. man according to Shohl is recorded in table 1.

The magnesium content of soft tissues by various estimates then ranges from about 600 to 825 mEq. The predominantly intracellular location corresponds exactly to that of potassium.

Magnesium has graded effects on central and peripheral nerves. Neuromuscular transmission and the stimulating effect of both potassium and acetylcholine on the motor end-plate are blocked by excessive magnesium. Magnesium prolongs the PR conduction time and widens the QRS complex. Intense vasodilatation occurs and blood pressure begins to fall at relatively low concentrations. Calcium counteracts both central and peripheral effects of magnesium.[6] The hypnotic and paralytic effects of magnesium are manifest at levels of magnesium of about 10 mEq./L.[7]

Magnesium has been found to be necessary for the action of many enzyme systems.[8] Perhaps the most prominent of these are many of the adenosine triphosphate (ATP) reactions. Examples include the hexokinase reaction, the formation of creatine phosphate in muscle, and the entrance of pyruvate

* Presented at the Thirty-eighth Annual Session of The American College of Physicians, Boston, Massachusetts, April 12, 1957.

From the Medical Service of the Veterans Hospital, Minneapolis, Minnesota, and the Department of Internal Medicine, The University of Minnesota.

Requests for reprints should be addressed to Edmund B. Flink, Veterans Hospital, Minneapolis 14, Minn.

into the tricarboxylic acid cycle. The formation of certain nucleotides, including triphosphopyridine nucleotide (TPN) and flavine adenine dinucleotide (FAD), is also magnesium- and ATP-dependent. Other ATP reactions also require magnesium. It is also important in ammonia metabolism, as exemplified by the need for it in the formation of urea in the ornithine cycle and the formation of glutamine from glutamic acid and ammonia. The action of cholinesterase and enteric phosphatase is enhanced by it. These are just examples of the many enzyme reactions which require magnesium. It is not surprising that magnesium has an intracellular position in view of the large portion of cellular metabolism which is partially dependent on its presence.

The results of magnesium deficiency in experimental animals [9, 10] and domestic animals [11] have been summarized in previous publications.[12, 13] The rate of development and severity of manifestations depend on the age, the species, and the extent of dietary restriction of magnesium. The neuromuscular signs include vasodilatation, irritability, spontaneous and noise-induced convulsions in small animals, and nervousness, restlessness, muscle twitching, unsteady gait and convulsions in large animals. Growth stops.

TABLE 1

Magnesium Content of the Human Body

	Gm.	mEq.
Skeleton	11.0	910.0
Cells	9.5	785.0
Extracellular water	.5	41.0
	21.0	1,736.0

Half of the animals die during the first convulsion. Increasing the calcium, potassium or nitrogen in rations enhances the severity and the rapidity of the development of magnesium deficiency.[10, 14]

Pathologic lesions have been found in many organs of animals dying of experimental magnesium deficiency. It is probable that the basic lesion is an inflammatory reaction in loose mesenchymal tissue.[15] The Purkinje cells of the cerebellum of birds,[16] rabbits and rats [17] have been found to exhibit chromatolysis, swelling, vacuolization of cells, and decrease in Nissl staining. It may be significant that one of the major pathologic changes in severe chronic alcoholism is cerebellar degeneration.[18] Tubular degeneration and calcification of the corticomedullary region and changes in the glomerular capsule occur in kidneys of rats, rabbits, hamsters and calves.[18, 19, 20] The concentration of calcium increases greatly in the kidneys. Fatty metamorphosis of liver cells and fibroblastic proliferation in livers of rats and calves [19, 20] and myocardial hemorrhages and calcification in calves' hearts [20] have also been found. Blaxter, Rook and MacDonald [21] consider all of the changes as being nonspecific and purely secondary to convulsions and anoxia.

A summary of some of the magnesium concentrations of tissues in animals with severe deficiency is recorded in table 2. In immature rats the magnesium content of bone decreased to 66% of normal in the study of Watchorn and McCance,[22] and to about 60% of normal in the study of Duckworth and Godden.[23] In a later study, after 10 days of re-alimentation with magnesium, the bone concentration had returned only about two-thirds of the way toward normal.[24] The authors also showed that a high calcium intake impaired the release of magnesium from the skeleton.[23] Kleiber, Boelter and Greenberg [25] pair-fed control and magnesium-deficient animals and found the carcass magnesium was just one-half of that in control rats.

TABLE 2

A Summary of Tissue Magnesium Concentrations in Normal Control Animals and in Animals with Magnesium Deficiency

Authors	Animals	Tissue	Units	Normal	Mg^{++} Deficiency
Cotlove, Holliday, Schwartz and Wallace[5]	8 rats	Muscle	mEq./Kg. F.F.T.*	22.3±0.3	20.4±0.4
			mEq./L. cell water	34	32
Tufts and Greenberg[10]	34 rats	Muscle	mg./100 gm.T†	29.6±.79 (24.6–35.1)	26.5±3.1 (15.2–33.5)
	22 rats	Brain	mg./100 gm.T†	16.6±2.54 (13.2–19.8)	13.6±2.17 (11.0–20.6)
	10 rats	Plasma	mg./100 ml.	3.08	1.42
Watchorn and McCance[22]	3 rats	Brain	mg./100 gm.T†	19.6±1.76	18.8±1.6
	8 rats	Muscle	mg./100 gm.T†	27.9±3.16	26.8±5.7
	5 rats	Heart	mg./100 gm.T†	24.2±5.38	22.4±4.6
	9 rats	Serum	mg./100 ml.	4.26	2.01
	10 rats	Bone ash	%	.38±.04	.20±.04
	3 rats	Teeth	%	1.0	.55
Blaxter, Rook and MacDonald[21]	Calves	Infra-spinatus	mg./100 gm.T†	18.0	15.9
	3 normal				
	4 defic.	Rectus femoris		20.2	18.5
		Diaphragm		19.1	18.8
		Supra-spinatus		18.4	19.2
		Heart		19.0	21.3

* Fat-free fresh tissue.
† Fresh tissue.

These rats were immature and growing. The adult human skeleton probably is not so ready a source of magnesium to supply the needs of the body as is the skeleton of an immature animal. In table 2 the differences from normal are small, but some individual concentrations in deficient animals are very much lower than any normal.

METHODS

The determination of magnesium in serum and urine was carried out by a modification of Garner's adaptation of Kolthoff's titan yellow reaction

with magnesium.[26] A series of normal subjects and patients without neurologic manifestations was studied and the mean value was 2.27 ± 0.26 mEq./L. Partial balance data were obtained measuring only the urine output of magnesium and the parenteral dose of magnesium sulfate. A large group of patients with chronic alcoholism and tremulousness and a few postoperative patients and patients with pyloric obstruction and alkalosis were studied. The clinical course of two alcoholic patients, one postoperative patient and one patient with severe metabolic alkalosis is reported in detail to illustrate manifestations of magnesium deficiency.

Results of Clinical Studies

A group of 29 patients with tremor and delirium of varying severity was studied. The mean serum level for this group was 1.58 ± 0.3 mEq./L. In a group of 21 patients with tremor and muscular twitchings but without delirium the mean magnesium level was $1.88 \pm .4$ mEq./L. These results correspond well to our previous experience.[12, 13]

Case Reports

Case 1. L. W. S., a 70 year old white male, was admitted to the University of Minnesota Hospitals and had a ureteral transplant into an ileal loop on December 19, 1955. He had continuous nasogastric suction for 12 days postoperatively, and had an average intake of 4,300 ml. water per day and gastroduodenal drainage of 2,240 ml. per day. Adequate amounts of potassium and sodium salts were given. On the seventh postoperative day the patient became confused and occasionally belligerent. His abdomen became distended. He had a fever with temperature as high as 103.8° F. He exhibited athetoid and choreiform movements, and tremor and twitching of muscles of the whole body. Serum sodium was 146 mEq./L.; serum potassium, 4.6 mEq./L.; serum calcium, 7.9 mg. per 100 ml. at a time when the serum albumin was 2.0 gm. and globulin 3.6 gm. per 100 ml. Serum magnesium on the eleventh postoperative day was 1.46 mEq./L. Magnesium sulfate (50% solution) was given intramuscularly in divided doses so that a total of 16 gm. (131 mEq. Mg^{++}) was given in three days. Disorientation, confusion and tremor stopped in 36 hours; gastric drainage could be stopped, and the patient began eating. He was weak and somewhat depressed and had a poor appetite, but he continued to improve from this time on.

Comment: This patient was seriously ill and was becoming worse clinically until magnesium therapy was started. The important clinical features were neuromuscular manifestations and moderate delirium, which cleared in 36 hours after magnesium therapy.

Case 2. G. B., a 59 year old white male, was admitted to the Minneapolis Veterans Hospital on September 30, 1956. He had severe hepatic cirrhosis with ascites and jaundice due to chronic alcoholism. On admission he was incontinent, confused, noisy, restless and disoriented, and had tremor and twitching of muscles. He was given meprobamate, 400 mg. four times a day, and chlorpromazine, 50 mg. three times a day, from the time of admission. His delirium became more severe and by the third day he was semicomatose. He was given 5.0 gm. of magnesium sulfate (41.5 mEq. Mg^{++}) and 40 mEq. of potassium chloride intravenously on the third day. The

following day he spoke coherently and was oriented and coöperative but still tremulous. From the fourth through the sixth day he was given 1.0 gm. of magnesium sulfate (8.2 mEq. of Mg^{++}) intramuscularly four times a day. He remained oriented and coöperative. By the eighth day he was confused again. His serum magnesium was 1.42 mEq./L. at this time. He was given 1.0 gm. of magnesium sulfate (8.2 mEq. of Mg^{++}) intramuscularly every four hours from the ninth to the twelfth day, and then every six hours for the next eight days. He became oriented and remained so 24 hours after magnesium was given again. He was able to leave the hospital on November 6, 1956.

Comment: This patient became very ill in spite of meprobamate and chlorpromazine. His course was favorably influenced twice by magnesium therapy. The first course of treatment was too short, resulting in relapse.

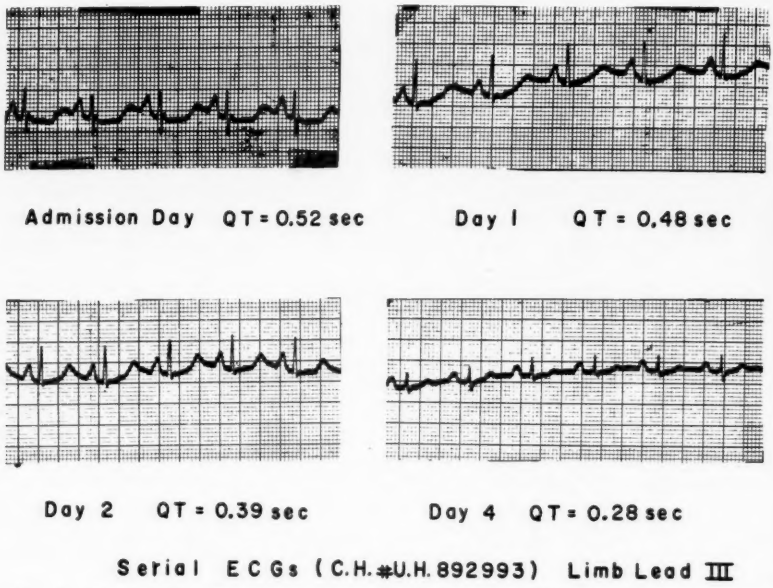


FIG. 1. *Case 3.* Serial electrocardiograms of patient, C. H. (case 3), are represented by limb lead 3. Refer to figure 2 for electrolyte concentrations on the days represented by these electrocardiograms.

This phenomenon of relapse as a result of too short a course of treatment has been observed a number of times.[12] His mental and neuromuscular manifestations were characteristic of those we are ascribing to magnesium deficiency.

Case 3. C. H., a 48 year old male, was admitted to the University of Minnesota Hospitals on January 30, 1956. He had noted constant vomiting and muscle cramping for one week. In 1942 he had suffered a perforation of a duodenal ulcer and had had intermittent partial obstruction for the ensuing 14 years. Severe epigastric pain with radiation into the back had begun three months prior to admission. He was

TABLE 3

Case 3 (C. H.) Approximate Balance of Sodium, Potassium and Chloride for the First Five Days as Measured by Total Fluid Intake and Output in Urine and Gastric Drainage. The values are recorded in milliequivalents.

	Sodium mEq.	Potassium mEq.	Chloride mEq.
Intake	1,356	869	2,771
Gastric output*	506	116	1,218
Urine output†	832	316	460
	+18	+437	+1,093

* The electrolyte concentrations of days 3 and 5 are estimated from days 2 and 4. The volumes for these days were accurately measured and recorded.

† The concentrations of electrolytes in the urine of day 4 are estimated from values of days 3 and 5. The volume of urine was carefully measured and recorded.

thin and deeply pigmented. He had carpopedal spasm with rigid flexion of the elbows. The neck was stiff, and a Chvostek sign was elicited. The abdomen was distended, and a succussion splash was easily elicited. Initial laboratory examinations: blood urea nitrogen, 94 mg. per 100 ml.; sodium, 140 mEq./L.; potassium, 3.4 mEq./L.; CO_2 capacity, 64 mEq./L.; chloride, 31 mEq./L.; hemoglobin, 15.5 gm. per 100 ml.; ultrafiltrable calcium, 3.6 mg. per 100 ml.; total calcium, 9.2 mg. per 100 ml. An electrocardiogram showed changes typical of hypopotassemia, with a QT interval of .52 sec., ST interval and T wave distortion, and prominent U waves. The serial changes in the electrocardiogram are recorded in figure 1. The initial serum magnesium was 2.27 mEq./L., but after 3 L. of fluids, administered intravenously, it had dropped to 1.32 mEq./L. Several hours after admission and shortly

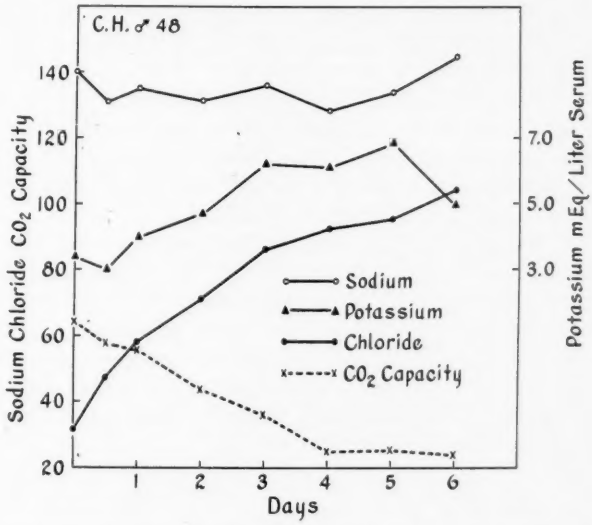


FIG. 2. The concentrations of serum electrolytes in mEq./L. of patient, C. H. (case 3), are plotted. Refer to table 3 for record of balance of sodium, potassium and chloride during this period.

after 1.0 gm. of calcium gluconate had been administered intravenously a grand mal seizure occurred. The calcium had apparently relieved the carpopedal spasm partially. Three more grams of calcium gluconate were administered and the carpopedal spasm was partially relieved a second time, but the patient had convulsions again soon after the calcium injection. Magnesium sulfate in a dose of 4.0 gm. (33 mEq. of Mg^{++}) was given intravenously in 1,000 ml. infusion mixture on the first day after the convulsions occurred. He was also given 1.0 gm. of magnesium sulfate intramuscularly four times on the second day. Disorientation and opisthotonos and positive toe signs became evident on the second day. On the third day choreo-athetoid movements appeared and the disorientation continued. On the fourth day severe delirium had developed. Magnesium sulfate therapy (2.0 gm. per day intramuscularly) was started at 10 p.m. on the fifth day and continued until the fourteenth day. Thirty-six hours after the start of magnesium therapy the sensorium cleared a great deal and remained completely clear starting on the eighth day. On the eighth day there was no gastric residual for the first time. On the twenty-fifth day his condition was very good and he had a gastrectomy. Unfortunately, an anastomotic leak developed and he died of peritonitis on the forty-fifth day. Table 3 summarizes the electrolyte therapy for the first five days, and figure 2 shows the course of electrolyte concentrations for five days. The concentrations of electrolytes in the gastric fluid and urine were estimated from values which bracketed the missing data, as indicated in the table. The estimates do not decrease the general significance of approximate balance, since it is unlikely that the actual value would affect the balances by more than $\pm$ 100 mEq., and probably not more than $\pm$ 50 mEq.

Comment: This patient had a metabolic alkalosis of unprecedented severity. The clinical course was very complicated, and criticism might be directed at the use of this case history, but certain provocative features make it desirable. The retention of potassium and chloride was very great, but there was little retention of sodium. Using his original and final chloride concentrations and approximate extracellular fluid volume, we estimated that he had a chloride deficit of about 940 mEq. His actual positive chloride balance was about 1,095 mEq. The possible adverse effect of calcium infusion may be related to the phenomenon of accentuating manifestations, including onset of convulsions in experimental animals with magnesium deficiency by high calcium intake.[14] He also received NH_4Cl intravenously during the first four days. We have shown that ammonium chloride has adverse effects on patients with liver disease and low serum magnesium.[13] When hydration was begun, the initially normal serum magnesium level dropped precipitously to a significantly low level. This phenomenon occurs often and helps to explain initial normal levels, which are confusing when they occur in patients with manifestations such as those described herein. The actual increase in delirium by the fifth day, when the other electrolytes were normal, is similar to that in case 4 and the apparent response to magnesium therapy is noted.

Case 4. T. L., a 34 year old white male, was admitted to the Abbott Hospital in Minneapolis on January 3, 1957. He had had a colon resection for diverticulitis in 1956. He admitted excessive use of alcohol. He was very weak, and fell in the bathroom on the second day. Then he was so weak he couldn't turn in bed. He was confused and noisy, and had auditory hallucinations. He was found to have a

marked hypopotassemic alkalosis, with a serum potassium of 0.8 mEq./L., sodium, 142 mEq./L., and chloride, 76 mEq./L. The CO_2 capacity was 35 mEq./L. two days later, when the chloride was 99 mEq./L., calcium, 11.2 mg. per 100 ml., and inorganic phosphorus, 1.2 mg. per 100 ml. Vigorous therapy with potassium salts (80 mEq. the first day and 160 mEq./day for four days) resulted in clearing of sensorium for one day and a return of muscle power. Two days after the start of potassium therapy he had a return of severe delirium, accompanied now by facial grimacing, generalized muscle twitching, tremor, and purposeless movements. A serum magnesium was 1.69 mEq./L. at this time. Two grams of magnesium sulfate (16.5 mEq. of Mg^{++}) were given intramuscularly every two hours four times, and then 1.0 gm. was given every six hours for four days. Definite improvement was noted in all symptoms in 8 hours. Confusion and tremor had cleared completely 46 hours after starting therapy. Recovery was uneventful after this.

Comment: Severe hypopotassemic alkalosis was corrected, with disappearance of severe muscular paresis. Although delirium temporarily decreased as the hypopotassemia was corrected, it became much worse, and tremor and other neuromuscular signs appeared. These cleared rather dramatically when magnesium was administered. The development of neuromuscular manifestations in cases 3 and 4 when hypopotassemia was being corrected has been observed previously,[12] and may well be related to the experimental observation that potassium accentuates the manifestations of magnesium deficiency.[14]

Balance Studies

By measuring the parenteral dose of magnesium and its excretion in the urine, we carried out partial balance studies on three patients with chronic alcoholism and moderately severe manifestations such as tremor, muscular

Table 4

Partial Balance Studies

The Total Magnesium Dose Administered Intramuscularly and the Total Magnesium Excreted in the Urine during Therapy Are Recorded

Pt.	Weight Kg.	Days	Initial Serum Mg^{++} mEq./L.	Mg^{++} I.M. mEq.	Urine Mg^{++} mEq.	Retained Mg^{++} mEq.
J. L.	86	6	1.43	199	119	80
F. K.	63	4	2.24	233	172	61
O. W.	62	7	2.08	365	256	109

twitching and delirium of mild degree. The results are recorded in table 4. Magnesium salts given parenterally are not retained by the normal subject, but all the administered magnesium appears in the urine.[7, 27] However, in a study on magnesium depletion in man by Fitzgerald and Fourman,[27] 25% and 45% of injected magnesium in three doses in two days, and five doses in three days, respectively, were retained in the two subjects. These facts give significance to the large positive balance for magnesium in these three

patients. Since these studies do not take into account the amount appearing in the urine from normal sources, the balances may actually be greater than recorded here. Studies are in progress now carrying on total balances on patients with chronic alcoholism and tremulousness.

Discussion

The manifestations we have ascribed to magnesium deficiency in patients can be listed as follows: muscular twitching and tremor, which may be mild or severe, with marked choreiform and athetoid movements, and may be so severe that all fine movements, such as handwriting, may be impossible; rarely, carpopedal spasm and positive Chvostek's and Trousseau's signs; profuse sweating; tachycardia and, occasionally, fever; mild anxiety to severe agitation; mild to severe delirium with hallucinations, confusion and disorientation, abusive language and maniacal behavior; finally, convulsions and coma. Not all patients have all the symptoms and signs listed, but, when one of these is severe, others are apt also to be severe.

There are a number of features which need to be clarified. There are undoubtedly multiple deficiencies in some patients, and particularly vitamin and potassium deficiency. The course of a number of patients can be cited as evidence that correction of potassium deficiency unmasks magnesium deficiency, as in cases 3 and 4 and in previous experience.[12]

There are patients who have low serum levels of magnesium and have no detectable symptoms or signs. On the other hand, there are patients with magnesium concentrations in the normal range who, despite this, have severe manifestations. The observations on case 3 emphasize the fact that the initial magnesium concentration may be spuriously high. This has also been found to be the case in patients with diabetic acidosis.[28, 29] Despite even a high level initially, it has been demonstrated that there is an actual magnesium deficit in diabetic acidosis.[29, 30] An identical situation exists in regard to potassium. The partial balances reported above also indicate that considerable magnesium was retained in two patients (F. K. and O. W., table 4) in spite of normal serum concentrations. Such observations are compatible with the view that the essential biochemical defect is a cellular depletion, and that the extracellular concentration is only a poor mirror of this cellular deficit. The skeletal reservoir is a completely unknown quantity in adult humans at present. The extracellular concentration is of importance, certainly, in considering the effects of high concentrations, just as it is in potassium intoxication. The response to treatment in a matter of hours to a day or two also favors the concept that the major manifestations are related to a cellular deficit. Hypocalcemic symptoms which are clearly due to decreased extracellular fluid concentration respond to intravenously administered calcium in a few minutes. Duckworth, Godden and Warnock [31] state: "Our results agree better with such a view (that of Greenberg and Tufts [32] favoring cellular deficit) than with the conception that the tetany

of magnesium deficiency is the outcome of disturbances of tissue fluid composition arising from deficiency."

A good response of patients with neuromuscular symptoms and signs attributed to magnesium deficiency has been reported by Hirschfelder and Haury,[33] Miller [34] and Suter and Klingman.[35] The responses of our patients have often been dramatic in the course of from four to eight hours, and usually have been clear-cut in the course of a day or two, but an occasional patient has responded only after three to four days. The experimental finding of slow or delayed response [21, 24, 32] to magnesium repletion fits in with this observation. There may be multiple factors which are as yet unexplained.

It has been found that the following schedule of intramuscular injection of magnesium sulfate is safe and does not result in hypnotic levels of magnesium when renal function is adequate: 2.0 gm. of magnesium sulfate (4 c.c. of 50% solution) every six hours for one day, followed by 1.0 gm. every six hours for from three to five days. If magnesium sulfate is given intravenously, it is best to distribute the above total dose for a day in all the parenteral fluids for that day. The maximal dose should be 5.0 gm. in 1,000 ml., given in not less than three hours.

Certain quantitative data need to be considered. Levey et al.[36] showed that two surgical patients sustained a negative balance of 26.5 mEq. and 22.4 mEq., respectively, without developing symptoms. Fitzgerald and Fourman [27] were able to deplete two normal males of 42 mEq. and 72 mEq. without a fall in serum magnesium and without development of symptoms. These two studies emphasize the fact that a modest negative balance of magnesium does not result in symptoms. It is significant that the serum magnesium did not fall in the latter study, and this suggests at least one or possibly several differences from the patients we reported above. The majority of patients with characteristic symptoms have serum levels below normal, suggesting that depletion had gone further than experimental depletion. Another additional possibility is that other chemical factors, including ammonia, potassium and calcium, plus the effect of withdrawal of a sedative agent (in the alcoholic patients), are added to the magnesium deficiency and act synergistically. Multiple deficiencies certainly exist in many alcoholic patients.

The pathogenesis of magnesium depletion remains obscure. One important factor is the simple deficient intake of magnesium during prolonged periods of parenteral fluid administration and gastrointestinal drainage, or during prolonged alcoholic bouts where alcohol constitutes the chief source of calories.

Another factor which needs further amplification is that of aldosterone. It has been clearly demonstrated that hypomagnesemia and a negative magnesium balance have been found in primary aldosteronism.[37] One can speculate that conditions such as cirrhosis with ascites and toxemia of preg-

nancy, which have been shown to have secondary aldosteronism, have a tendency to magnesium depletion because of an aldosterone effect.

Summary and Conclusions

A clinical syndrome characterized by muscle tremor, twitching and more bizarre movements, occasionally by convulsions and often by delirium, has been described and is considered to be a manifestation of magnesium deficiency. The evidences for this concept are the many similarities to experimental animal magnesium deficiency, the occurrence of low mean serum magnesium concentrations for a group of patients, a positive magnesium balance during treatment, and, finally, the frequently gratifying and sometimes dramatic response to therapy with magnesium salts.

Acknowledgments

We wish to thank Dr. C. D. Creevy for permission to report case 1, Dr. F. Goetz for permission to report case 3, and Dr. T. Lowry for permission to report case 4. We wish also to acknowledge the technical assistance of Mrs. Marilyn G. Goodsell, Miss Ruth Engst and Miss Iris Noma.

Summario in Interlingua

Es describite un syndrome clinic de tremor muscular, tic, bizarre movimentos sin motivation apparente, delirio, e a vices convulsiones. Iste syndrome es considerate como un manifestation de carentia de magnesium. Es reportate quatro casos pro illustrar varie aspectos del problema e specialmente pro signalar le variabilitate del manifestationes, insimul con le facto que un correction del depletion de kalium pote dismascar le supra-mentionate manifestationes, que calcium e ammoniaco pote accentuar le symptomas, e que le responsa al therapia es frequentemente satisfacente. Le manifestationes clinic es simile al manifestationes del carentia experimental de magnesium in animales. Le nivello medie de magnesium in 29 patientes con delirio e disturbation neuromuscular esseva 1,58 mEq/l, comparate con 1,88 mEq/l in 21 patientes con disturbationes neuromuscular sed sin delirio e 2,27 mEq/l in un gruppo de individuos normal. Studios incomplete del balancia indicava un retention de inter 60 e 109 mEq de magnesium in tres patientes con manifestationes neuromuscular e leve grados de delirio. Le manifestationes es clarmente differente ab tetania causate per hypocalcemia o alcalosis. Durante le therapia le manifestationes dispare gradualmente, lo que suggere que le deficit es intracellular o que un defective processo metabolic es gradualmente reparate.

BIBLIOGRAPHY

1. Shohl, A. T.: Mineral metabolism, 1939, Reinhold Publishing Co., New York, pp. 19, 20.
2. Widdowson, E. M., McCance, R. A., and Spray, C. M.: The chemical composition of the human body, Clin. Sc. **10**: 113–125, 1951.
3. Duckworth, J., and Warnock, G. M.: The magnesium requirements of man in relation to calcium requirements, with observations on the adequacy of diets in common use, Nutrition Abstr. and Rev. **12**: 167–183, 1942.
4. Gilder, H., Redo, S. F., Barr, D., and Child, C. G.: Water distribution in normal subjects and in patients with Laennec's cirrhosis, J. Clin. Investigation **33**: 555–564, 1954.
5. Cotlove, E., Holliday, M. A., Schwartz, R., and Wallace, W. M.: Effect of electrolyte depletion and acid-base disturbance on muscle cations, Am. J. Physiol. **167**: 665–675, 1951.

6. Engbaek, L.: Pharmacological actions of magnesium ions, Pharmacol. Rev. **4**: 396–410, 1952.
7. Smith, P. K., Winkler, A. W., and Hoff, H. E.: The pharmacological actions of parenterally administered magnesium salts, Anesthesiology **3**: 323, 1942.
8. White, A., Handler, P., Smith, E. L., and Stetten, DeW., Jr.: Principles of biochemistry, 1954, McGraw-Hill Book Co., New York.
9. Kruse, H. D., Orent, E. R., and McCollum, E. V.: Studies on magnesium deficiency in animals. I. Symptomatology resulting from magnesium deprivation, J. Biol. Chem. **96**: 519–539, 1932.
10. (a) Tufts, E. V., and Greenberg, D. M.: The biochemistry of magnesium deficiency. I. Chemical changes resulting from magnesium deprivation, J. Biol. Chem. **122**: 693–714, 1938.
(b) Tufts, E. V., and Greenberg, D. M.: The biochemistry of magnesium deficiency. II. The minimum magnesium requirement for growth, gestation and lactation and the effect of the dietary calcium level thereon, J. Biol. Chem. **122**: 715–726, 1938.
11. Sjollema, B.: Nutritional and metabolic disorders in cattle, Nutrition Abstr. and Rev. **1**: 621–632, 1932.
12. Flink, E. B., Stutzman, F. L., Anderson, A. R., Konig, T., and Fraser, R.: Magnesium deficiency after prolonged parenteral fluid administration and after chronic alcoholism complicated by delirium tremens, J. Lab. and Clin. Med. **43**: 169–183, 1954.
13. Flink, E. B.: Magnesium deficiency syndrome in man, J. A. M. A. **160**: 1406–1409, 1956.
14. (a) Colby, R. W., and Frye, C. M.: A. Effect of feeding various levels of calcium, potassium and magnesium to rats, Am. J. Physiol. **166**: 209, 1951.
(b) Colby, R. W., and Frye, C. M.: B. Effect of feeding high levels of protein and calcium in rat rations on magnesium deficiency syndrome, Am. J. Physiol. **166**: 408–412, 1951.
15. Lowenhaupt, E., Schulman, M. P., and Greenberg, D. M.: Basic histologic lesions of magnesium deficiency in rat, Arch. Path. **49**: 427–433, 1950.
16. Bird, F. H.: Magnesium deficiency in chick: clinical and neuropathologic findings, J. Nutrition **39**: 13–29, 1949.
17. Barron, G. P., Brown, S. O., and Pearson, P. B.: Histologic manifestations of magnesium deficiency in rat and rabbit, Proc. Soc. Exper. Biol. and Med. **70**: 220–223, 1949.
18. Neubuerger, K. T.: The changing neuropathologic picture of chronic alcoholism, Arch. Path. **63**: 1–6, 1957.
19. Schrader, G. A., Prickett, C. O., and Salmon, W. D.: Symptomatology and pathology of potassium and magnesium deficiency in rat, J. Nutrition **14**: 85–109, 1937.
20. Moore, L. A., Hallman, E. T., and Scholl, L. B.: Cardiovascular and other lesions in calves fed diets low in magnesium, Arch. Path. **26**: 820–838, 1939.
21. Blaxter, K. L., Rook, J. A. F., and MacDonald, A. M.: Experimental magnesium deficiency in calves. 1. Clinical and pathological observations, J. Comp. Path. and Therap. **64**: 157–175, 1954.
22. Watchorn, E., and McCance, R. A.: Subacute magnesium deficiency in rats, Biochem. J. **31**: 1379–1390, 1937.
23. Duckworth, J., and Godden, W.: The lability of skeletal magnesium reserves. The influence of rates of bone growth, Biochem. J. **35**: 816–823, 1941.
24. Duckworth, J., and Godden, W.: The replenishment of depleted skeletal reserves of magnesium, Biochem. J. **37**: 595–598, 1943.
25. Kleiber, M., Boelter, M. D. D., and Greenberg, D. M.: Fasting catabolism and food utilization of magnesium deficient rats, J. Nutrition **21**: 363–372, 1941.
26. Garner, R. J.: Colorimetric determination of magnesium in plasma or serum by means of titan yellow, Biochem. J. **40**: 828–831, 1946.

27. Fitzgerald, M. G., and Fourman, P.: An experimental study of magnesium deficiency in man, Clin. Sc. **15**: 635–647, 1956.
28. Butler, A. M., Talbot, N. B., Burnett, C. H., Stanbury, J. B., and MacLachlan, E.: Metabolic studies in diabetic coma, Tr. A. Am. Physicians **60**: 102–109, 1947.
29. Nabarro, J. D. N., Spencer, A. G., and Stowers, J. M.: Metabolic studies in severe diabetic ketosis, Quart. J. Med. **21**: 225–248, 1952.
30. Martin, H. E., and Wertman, M.: Serum potassium, magnesium, and calcium levels in diabetic acidosis, J. Clin. Investigation **26**: 217–228, 1947.
31. Duckworth, J., Godden, W., and Warnock, G. M.: The effect of acute magnesium deficiency on bone formation in rats, Biochem. J. **34**: 97–108, 1940.
32. Greenberg, D. M., and Tufts, E. V.: The nature of magnesium deficiency, Am. J. Physiol. **121**: 416–423, 1938.
33. Hirschfelder, A. D., and Haury, V. G.: Clinical manifestations of high and low plasma magnesium, J. A. M. A. **102**: 1138–1141, 1934.
34. Miller, J. F.: Tetany due to deficiency in magnesium, Am. J. Dis. Child. **67**: 117–119, 1944.
35. Suter, C., and Klingman, W. O.: Neurologic manifestations of magnesium depletion states, Neurology **5**: 691–699, 1955.
36. Levey, S., Abbott, W. E., Krieger, H., and Davis, J. H.: Metabolic alterations in surgical patients. VIII. Studies involving iron and magnesium metabolism in patients with gastrointestinal drainage, J. Lab. and Clin. Med. **47**: 437–443, 1956.
37. Mader, I. J., and Iseri, L. T.: Spontaneous hypopotassemia, hypomagnesemia, alkalosis and tetany due to hypersecretion of a corticosterone-like mineralocorticoid, Am. J. Med. **19**: 976–988, 1955.

THE INFLUENCE OF GONADAL HORMONES ON SERUM LIPIDS AND LIPOPROTEINS: STUDIES IN NORMAL AND HYPOGONADAL SUBJECTS *

By Robert H. Furman, M.D., F.A.C.P., and R. Palmer Howard, M.D., F.A.C.P., *Oklahoma City, Oklahoma*

Clinicians have known for almost 200 years that the manifestations of coronary atherosclerosis are much more frequent in men than in women. Numerous autopsy studies have disclosed the disease in men earlier in life and in a more severe form than is the case with women, although anatomically this sex difference is somewhat less impressive than it is clinically. Autopsy studies on oophorectomized women, on the other hand, reveal an incidence and severity of coronary atherosclerosis more closely resembling that noted in men.[1, 2] Of interest and relevance are the opinions of White [3] and Gertler,[4] that there is less evidence of coronary atherosclerosis at autopsy in eunuchs than in noncastrate males.

Several reports over the past 10 years have described changes in serum cholesterol and phospholipid levels in human subjects following androgen or estrogen administration. These reports generally lead to the conclusion that estrogens reduce cholesterol or cholesterol-phospholipid ratios or both,[5-18] whereas androgens have the opposite effect.[18]

Since virtually all of the serum cholesterol and phospholipids circulate as lipid-protein complexes or lipoproteins, rather than as individual molecules of lipid, any study of the response of the serum lipids to hormonal or other agents or regimens must include qualitative and quantitative evaluation of serum lipoproteins if it is to be considered complete. Several methods are now available for the separation and measurement of the serum lipoproteins, and alteration of the human serum lipoprotein spectrum by gonadal steroid administration has been reported.[17-23]

The following remarks are based on data derived mainly from two studies, each covering a period of approximately four years. The first study involved 60 subjects who received androgens or estrogens over variable periods of time, usually for several months. These subjects included normal

* From the Symposium on the Pathogenesis of Coronary Heart Disease, presented at the Thirty-eighth Annual Session of The American College of Physicians, Boston, Massachusetts, April 10, 1957.

From the Cardiovascular and the Endocrinology and Metabolism Sections of the Oklahoma Medical Research Foundation, and the Department of Medicine, University of Oklahoma School of Medicine, Oklahoma City, Oklahoma.

This study was supported in part by research grants from the National Heart Institute (H-1429, H-1561 and H-1694) and the National Institute of Arthritis and Metabolic Diseases (A-179), the Oklahoma State Heart Association, the Ayerst Laboratories, New York, N. Y., and the Smith, Kline and French Foundation, Philadelphia.

Requests for reprints should be addressed to Robert H. Furman, M.D., The Oklahoma Medical Research Foundation, 825 Northeast Thirteenth Street, Oklahoma City 4, Oklahoma.

or hypogonadal men and women in general good health. Each subject served as his own control, and a variety of gonadal steroids, mainly oral preparations, was employed.[23] In most subjects weekly or biweekly samples of serum were obtained.

The second study was concerned with 24 eunuchs and 20 noncastrate controls who were matched with respect to age and body build as closely as the distribution of individuals in the available population would permit. These castrate and noncastrate subjects were living together in an institution for the mentally deficient. Samples of serum in this study were obtained at intervals of several months over a three-year period. Five samples of

TABLE 1

Comparison of Lipoprotein Class Designations According to Methodology

Absolute identity of comparable fractions is not implied

Ultracentrifugation Solvent Density 1.063 Sf	1.21 $-S_{1.21}$	Electrophoresis Paper pH 8.6 Ionic strength 0.05 Zone		Cohn Fractionation Method 10 Fractions
400–40,000	>70	Origin lipid	Not observed	
20–400[2]				
12–20[2]	40–70	beta$_1$	alpha$_2$[1]	I + III
0–12[3]	25–40		beta$_1$	
	20–25	"alpha$_2$"		
	0–20	alpha$_1$	alpha	IV + V + VI

(1) Mean density about 1.00, i.e., slightly lighter than serum. Alpha$_2$ shows some variation in position with age of serum and technic, and occasionally may contain the $-S_{1.21}$ 20–25 fraction. There appears to be some parallelism between height of alpha$_2$ peak (by zone electrophoresis) and the neutral fat content of the native serum.

(2) S_f 12–400 fraction contains lipoproteins of density less than 1.019 gm./ml.

(3) S_f 0–12 or $-S_{1.21}$ 25–40 contains lipoproteins of density between 1.019 and 1.063 gm./ml.

For further details regarding methodology and the content of these several fractions, the reader is referred to Kunkel and Trautman (J. Clin. Investigation **35**: 641, 1956), and Havel, Eder and Bragdon (J. Clin. Investigation **34**: 1345, 1955), and to Cohn et al. (J. Am. Chem. Soc. **62**: 465, 1950).

blood were obtained from each eunuch (with a few exceptions), and four from each control subject.

METHODS

Serum cholesterol and phospholipid levels were determined by the methods of Sperry and Webb [24] and by a modification [25] of the method of Youngburg.[26] The factor of 25 was used to convert lipid phosphorus to phospholipid.

Serum lipoproteins were determined by ultracentrifugation at a solvent density of 1.21 gm. per milliliter according to the method of Lewis, Green and Page.[27] The extent to which serum lipoproteins undergo flotation when this technic is utilized is virtually complete.[28] In healthy subjects two major lipoprotein fractions are noted: a high density lipoprotein fraction with a flotation rate of $-S_{1.21}$ 0–20, which is similar to, if not identical with, "alpha" lipoprotein as determined by electrophoresis; and a lower density

lipoprotein fraction with a flotation rate of $-S_{1.21}$ 25–40 or 25–70, which probably corresponds to "beta" lipoprotein. The $-S_{1.21}$ 25–40 lipoprotein fraction corresponds to the S_f 0–12 fraction of Gofman and the $-S_{1.21}$ 40–70 to the S_f 12–20 fraction (table 1).

In most of the subjects in these two studies, urinary 17-ketosteroid and gonadotropin excretion was measured, employing methods previously described.[23]

Results

The high density $-S_{1.21}$ 0–12 ("alpha") lipoprotein fraction and the ratio of high density to lower density lipoprotein, i.e., the alpha/beta lipoprotein ratio, proved extremely sensitive to gonadal steroid administration, *increasing* in concentration and value regularly and significantly when estrogen was given, *decreasing* regularly and significantly when androgen was

TABLE 2

Relation of Changes in Other Serum Lipids to High Density Lipoprotein Changes

		Opposite	No Change	Similar
$-S_{1.21}$ 25–40 ("Beta")	Androgen	56%	31%	13%
	Estrogen	46%	35%	19%
Total Cholesterol	Androgen	15%	42%	43%
	Estrogen	12%	61%	27%
Phospho-Lipid	Androgen	10%	40%	50%
	Estrogen	None	31%	69%

Lower density $-S_{1.21}$ 25–40 ("beta") lipoprotein concentrations usually underwent no change, or changed in the direction opposite to that of the high density $-S_{1.21}$ 0–12 ("alpha") lipoproteins when gonadal steroids were administered. Because of this, serum cholesterol levels either remained unchanged or varied with the high density fraction. This was also true of serum phospholipid concentrations. The greater tendency for phospholipid to vary with the high density fraction is undoubtedly due to the relatively low C/P ratio characteristic of high density lipoproteins. (Percentages based on changes observed when androgens were administered or discontinued 52 times, estrogens 26 times in 31 subjects.)

given (figures 1 and 2). These changes were often clearly discernible within 48 hours of initiating therapy; on the other hand, it was often two or more weeks before control values were reached, once treatment was discontinued. In subjects receiving gonadal steroids while on a constant diet as part of a metabolic balance study, nitrogen excretion returned to control values following discontinuance of androgen more promptly than did the serum lipoprotein levels.

Because the concentration of high density lipoprotein is significantly and consistently altered by gonadal steroid administration, it is practicable to relate the behavior of the other serum lipids and lipoproteins to that of the high density lipoproteins under these circumstances.

When high density (alpha) lipoprotein concentrations are altered by gonadal steroids, lower density (beta) lipoprotein concentrations usually

change in the opposite direction (figures 1 and 2). However, they may remain relatively unchanged or, less frequently, vary in the same direction as the high density lipoprotein (table 2).

The response of the serum total cholesterol and phospholipid concentrations appears to be determined by the nature of the responses of the major lipoprotein fractions—that is, if these fractions vary inversely when steroids are given, then the chemically-determined cholesterol and phospholipid levels

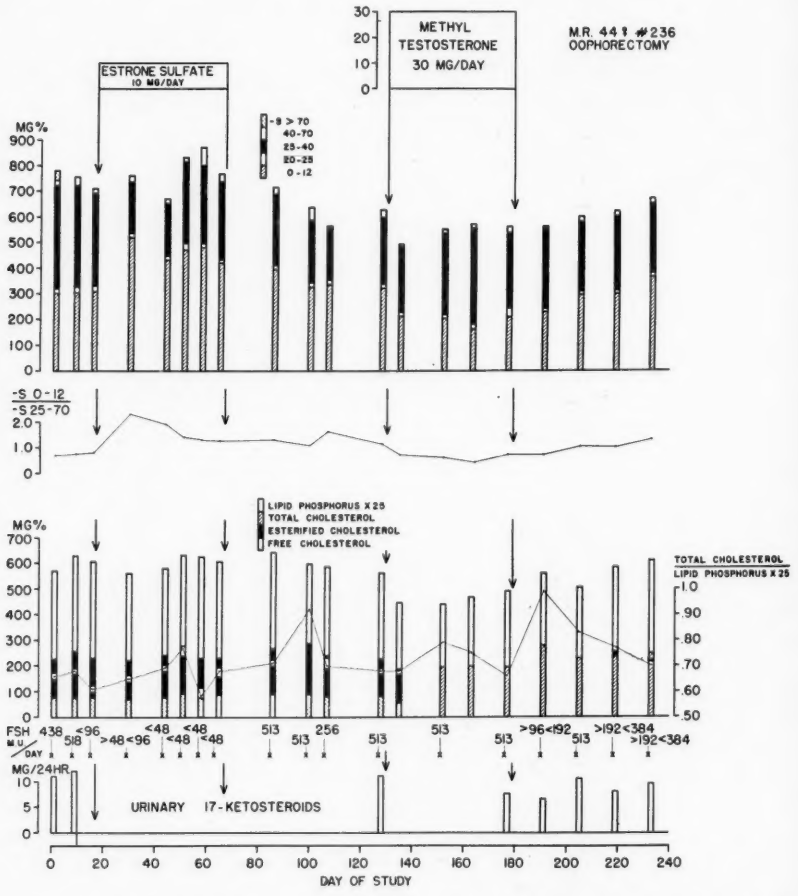


FIG. 1. M. R., 44 year old surgical castrate. Estrone sulfate, 10 mg./day, led to increased levels of $-S_{1.21}$ 0–12 lipoproteins and to increased values for the $-S_{1.21} \frac{0\text{–}12}{25\text{–}70}$ (alpha/beta) lipoprotein ratios. Methyltestosterone, 30 mg./day, produced the opposite effect. During methyltestosterone administration, serum cholesterol and phospholipid levels fell significantly (at 0.01 and 0.02 levels of significance, respectively). It is of interest to note the reduction in urinary gonadotropin excretion that accompanied estrogen administration.

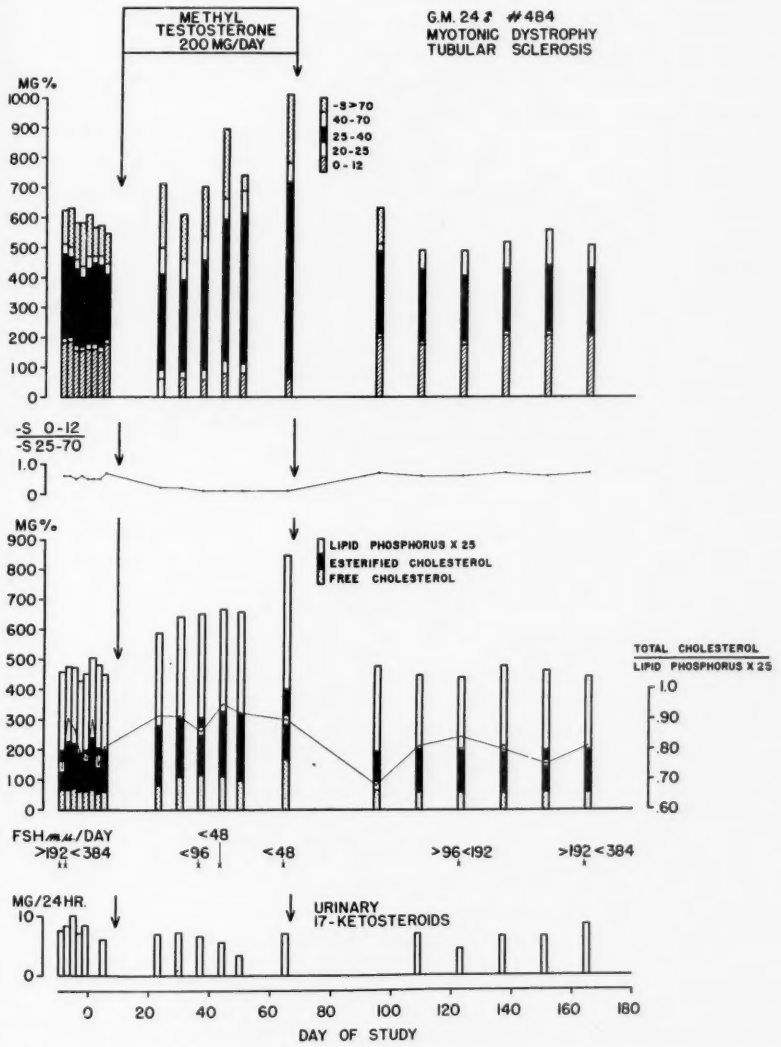


FIG. 2. G. M., 24 year old male with myotonic dystrophy and primary hypogonadism. Methyltestosterone, 200 mg./day, resulted in marked decrease in $-S_{1.21}$ 0–12 lipoprotein levels and in the values for $-S_{1.21}\frac{0-12}{25-70}$ ratios, and unusually marked increases in the lower density $-S_{1.21}$ 25–40 lipoprotein concentrations. The latter resulted in marked increases in serum cholesterol and phospholipid levels. It is of interest to note the reduction in urinary gonadotropin and 17-ketosteroid excretion during this period.

tend to remain relatively unchanged, although a greater tendency was noted for phospholipid levels to vary with the high density (alpha) lipoprotein fraction than was noted for cholesterol (table 2), presumably because of the relatively low C/P ratio characteristic of high density lipoproteins. (Infrequently, in association with relatively large doses of methyltestosterone, disproportionately large increases in the lower density (beta) lipoprotein concentrations were responsible for marked increases in serum total cholesterol and phospholipid levels (figure 2)). If change in the concentration of high density (alpha) lipoprotein is not accompanied by any change in the lower density lipoprotein, then the serum total cholesterol and phospholipid levels vary with the higher density fractions. Finally, if high and lower density lipoprotein fractions vary together, then the serum cholesterol and phospholipid levels obviously must change in the same direction as that of the major lipoprotein fractions. Actually, relatively little change in serum cholesterol or phospholipid levels is noted when the mean per cent change in concentration from control values is determined for a number of subjects receiving one or more courses of gonadal steroids (table 3).

TABLE 3

Relative Change in Serum Lipids Induced by Gonadal Steroids

	Cholesterol	Phospholipid	C/P Ratio	$-S_{1.21}$ 0–12 "Alpha"	$-S_{1.21}$ 25–40 "Beta"	Alpha/Beta	No. of Subjects	No. Courses Steroid
Androgen	101±6	93±4	107±2	47±4	134±10	40±3	18	27
Estrogen	106±4	116±3	91±3	135±5	94±5	150±10	12	17

Per cent change (relative to mean control values) induced in several serum lipid values by gonadal steroid administration. The changes indicated in this table are not necessarily maximal, since many of the subjects received only small doses of steroid, and statistical significance is therefore not shown. The figures following the per cent change represent standard error.

It is of interest that the lower density lipoprotein fractions corresponding to the S_f 12–20 or 20–100 fractions of Gofman showed no consistent response to gonadal steroid administration.

The results of our study of eunuchs are in conformity with data derived from the gonadal steroid study just described. Higher concentrations of high density (alpha) lipoproteins were found in eunuchs at each age level studied, i.e., 21 to 30, 31 to 50, and over 50 years of age. The high density/lower density (alpha/beta) lipoprotein ratios were significantly higher in the eunuchs at all age levels. Total cholesterol concentrations were significantly lower in the eunuchs only in the 21 to 30 age group, while phospholipid levels did not differ significantly at any age level.

DISCUSSION

The demonstration of this relationship between chemically determined lipids and the lipoproteins of the serum does not determine whether the

primary effect of gonadal steroids with respect to lipids is on the metabolism of the lipid molecule as such, or on some aspect of lipoprotein synthesis or degradation. Furthermore, we are not certain what determines the nature of the lower density (beta) lipoprotein response, although there appears to be a tendency for the lower density fraction to vary in a direction opposite to that of the high density fraction when relatively large doses of androgen are given.

Summary and Conclusions

It is clear from these studies that the serum high density (alpha) lipoproteins and the ratio of high density to lower density (alpha/beta) lipoproteins are sensitive indicators of change in gonadal hormone relationships. Increase in relative estrogenicity, whether by administering estrogen or withdrawing androgen, is always associated with increase in high density lipoprotein concentrations and high density/low density lipoprotein ratios. Increase in relative androgenicity has the opposite effect. The lower density (beta) lipoprotein response is more variable but usually opposite to that of the high density fraction.

Changes in chemically determined cholesterol and phospholipid levels appear to be determined by the nature of the changes in the major lipoprotein fractions under these conditions. On the other hand, absence of change in serum cholesterol or phospholipid levels does not preclude the possibility of major alteration of the lipoprotein spectrum.

Whether these serum lipoprotein-hormone relationships are causally related to the marked sex difference in the incidence of coronary artery disease remains to be determined by further study. There is good agreement among workers in this field that the concentration and physical status of the serum lipids have some etiologic significance in this disease. We feel, therefore, that further efforts in the direction of the studies described are warranted.

Summario in Interlingua

Depost quasi 200 annos, le clinicos sape que le manifestationes de atherosclerosis coronari es multo plus frequente in homines que in feminas. Proque le cholesterol e le phospholipidos del sero circula como complexos lipido-proteinic o lipoproteinas plus tosto que como moleculas de lipido, le autores ha studiate le responsa del lipoproteinas e lipidos seral a steroides gonadal in un gruppo de 60 subjectos in generalmente bon stato de sanitate. In plus, illes ha comparate le lipidos e lipoproteinas seral in un gruppo de 24 eunuchos e 20 non-castrate masculos de controlo.

Le lipoproteinas esseva determinate per ultracentrifugation con un densitate del solvente de 1,21 g per millilitro. In subjectos normal, duo major fractiones de lipoproteina es notate: Un fraction a alte densitate con un flottation de $-S_{1,21}$ 0–12 (lipoproteina "alpha") e un fraction a plus basse densitate con un flottation de $-S_{1,21}$ 25–40 o 25–70 (lipoproteina "beta"), correspondente al fractiones S_f 0–12 o 12–20 de Gofman.

Le fraction a alte densitate e le proportion alpha a beta (lipoproteina con alte a lipoproteina con basse densitate) se monstrava extrememente sensibile al administration de steroides gonadal. Lor concentration, respectivemente lor valor, se aug-

mentava regular- e significativemente quando estrogeno esseva administrate e se abassava regular- e significativemente quando androgeno esseva administrate. Quando le concentrationes de lipoproteina ("alpha") a alte densitate es alterate per steroides gonadal, le concentrationes de lipoproteina ("beta") a basse densitate es usualmente modificate in le direction contrari. Tamen, il occurre que illos remane relativemente stabile o, minus frequentemente, que illos varia in le mesme direction como le lipoproteinas a alte densitate. Le responsa del concentrationes de total cholesterol e phospholipido seral es apparentemente determinate per le natura del responsas del major fractiones de lipoproteina. In casos in que iste fractiones varia inversemente quando steroides es administrate, le nivellos de cholesterol e de phospholipido tende a remaner relativemente inalterate. Si le alteration del concentrationes de lipoproteina a alte densitate non es accompaniate de ulle alteration in le concentrationes del lipoproteina a basse densitate, alora le nivellos de cholesterol e de phospholipido seral varia con le fraction a alte densitate. Finalmente, si le fractiones de lipoproteina a alte densitate e a basse densitate varia insimul, alora le nivellos de cholesterol e de phopsholipido seral debe variar obviemente in le mesme direction como le major fractiones de lipoproteina. De facto, relativemente pauc alteration del nivellos de cholesterol e de phospholipido seral es a notar quando le alteration procentual medie in comparation con le nivellos de controlo es determinate pro un serie de individuos recipiente un o plure cursos de steroides gonadal.

Le fractiones de lipoproteina a basse densitate, correspondente al fractiones S_f 12–20 o 20–100, non monstrava un responsa uniforme al administration de steroides gonadal.

Le resultatos del studio de eunuchos es de accordo con le datos derivate ab le studio del steroides gonadal. Plus alte concentrationes del lipoproteinas ("alpha") a alte densitate esseva trovate in le eunuchos a omne etates studiate, e etiam le proportion alpha a beta (lipoproteina con alte a lipoproteina con basse densitate) esseva regular- e significativemente plus grande in le eunuchos de omne etates. Le concentrationes de cholesterol total esseva significativemente plus basse in eunuchos a etates de inter 21 e 30 annos, sed le concentrationes de phospholipido non differeva significativemente inter eunuchos e non-castratos a ulle etate.

Si o non iste relationes inter lipoproteina seral e hormones es connectite per un nexo causal con le marcate differentias sexual in le incidentia de morbo de arteria coronari remane a determinar per studios additional.

BIBLIOGRAPHY

1. Wuest, J. H., Dry, T. J., and Edwards, J. E.: The degree of coronary atherosclerosis in bilaterally oophorectomized women, Circulation **7**: 801, 1953.
2. Riven, A. U., and Dimitroff, S. P.: The incidence and severity of atherosclerosis in estrogen-treated males, and in females with a hypoestrogenic or hyperestrogenic state, Circulation **9**: 533, 1954.
3. White, P. D., discussion, *in* Barr, D. P., Russ, E. M., and Eder, H. A.: Influence of estrogens on lipoproteins in atherosclerosis, Tr. A. Am. Physicians **65**: 102, 1952.
4. Gertler, M. M.: Personal communication.
5. Eilert, M. L.: The effects of estrogens upon the partition of the serum lipids in female patients, Am. Heart J. **38**: 472, 1949.
6. Eilert, M. L.: The effect of estrogens upon the partition of the serum lipids in female patients, Metabolism **2**: 137, 1953.
7. Oliver, M. F., and Boyd, G. S.: The effect of estrogens on the plasma lipids in coronary artery disease, Am. Heart J. **47**: 348, 1954.
8. Oliver, M. F., and Boyd, G. S.: The influence of the sex hormones on the circulatory lipids and lipoproteins in coronary sclerosis, Circulation **13**: 82, 1956.

9. Barr, D. P., Russ, E. M., and Eder, H. A.: Influence of estrogens on lipoproteins in atherosclerosis, Tr. A. Am. Physicians **65**: 102, 1952.
10. Barr, D. P.: Some chemical factors in the pathogenesis of atherosclerosis, The George E. Brown Memorial Lecture, Circulation **8**: 641, 1953.
11. Barr, D. P., Russ, E. M., and Eder, H. A.: Protein-lipid relationships in plasma, *in* Blood cells and plasma proteins, edited by J. L. Tullis, 1953, Academic Press, New York.
12. Russ, E. M., Eder, H. A., and Barr, D. P.: Influence of gonadal hormones on protein-lipid relationships in human plasma, Am. J. Med. **19**: 4, 1955.
13. Steiner, A., Payson, H., and Kendall, F. E.: Effect of estrogenic hormone on serum lipids in patients with coronary atherosclerosis, Circulation **11**: 784, 1955.
14. Marett, W. C., and Vivas, J. R.: The effect of oral estrogens on serum cholesterol and total lipids, U. S. Armed Forces M. J. **4**: 1439, 1953.
15. Gitman, L., and Greenblatt, I. J.: Effect of intravenously administered estrogen in cardiovascular disease, Angiology **4**: 502, 1953.
16. Gertler, M. M., Hudson, P. B., and Jost, H.: Effects of castration and diethylstilbestrol on the serum lipid pattern in man, Geriatrics **8**: 500, 1953.
17. Robinson, R. W., Higano, N., Cohen, W. D., Sniffen, R. C., and Sherer, J. W., Jr.: Effects of estrogen therapy on hormonal functions and serum lipids in men with coronary atherosclerosis, Circulation **14**: 365, 1956.
18. Oliver, M. F., and Boyd, G. S.: Endocrine aspects of coronary sclerosis, Lancet *2*: 1273, 1956.
19. Barr, D. P.: Influence of sex and sex hormones upon the development of atherosclerosis and upon the lipoproteins of plasma, J. Chron. Dis. **1**: 63, 1955.
20. Furman, R. H., Howard, R. P., and Conrad, L. L.: A preliminary study of the influence of androgenic and estrogenic steroids on the ultracentrifugal and electrophoretic patterns of the serum alpha and beta lipoproteins and globulins in eunuchoid males and postmenopausal females, Am. J. Med. **16**: 594, 1954; Clin. Res. Proc. **2**: 126, 1954.
21. Furman, R. H., Howard, R. P., and Conrad, L. L.: Alterations in serum lipoprotein distribution induced by gonadal steroids: evidence of a regulatory role of these steroids in protein-lipid association, Clin. Res. Proc. **2**: 87, 1954.
22. Furman, R. H., Howard, R. P., and Conrad, L. L.: The influence of androgen and estrogen in the association of lipids with serum globulins, ultracentrifugal and electrophoretic studies of problems in atherosclerosis, J. Clin. Investigation **33**: 935, 1954.
23. Furman, R. H., Howard, R. P., Norcia, L. N., and Keaty, E. C.: Influence of androgens and estrogens and related steroids on serum lipids and lipoproteins: observations in hypogonadal and normal human subjects, Am. J. Med., in press.
24. Sperry, W. M., and Webb, M.: A revision of the Schoenheimer-Sperry method for cholesterol determination, J. Biol. Chem. **187**: 97, 1950.
25. Hawk, P. B., Oser, B. L., and Summerson, W. H.: Practical physiological chemistry, 12th Ed., 1947, The Blakiston Co., Philadelphia, p. 541.
26. Youngburg, G. E., and Youngburg, M. V.: Phosphorus metabolism. I. A system of blood phosphorus analysis, J. Lab. and Clin. Med. **16**: 158, 1930.
27. Lewis, L. A., Green, A. A., and Page, I. H.: Ultracentrifuge lipoprotein patterns of serum of normal, hypertensive and hypothyroid animals, Am. J. Physiol. **171**: 391, 1952.
28. Furman, R. H., Norcia, L. N., Fryer, A. W., and Wamack, B. S.: Lipoprotein recovery following ultracentrifugal fractionation at solvent density 1.21 as determined by cholesterol and lipid phosphorus analyses of supernatant and bottom fractions, J. Lab. and Clin. Med. **47**: 730, 1956.

USE OF A "DOUBLE-BLIND" STUDY INVESTIGATING THE CLINICAL MERITS OF A NEW TRANQUILIZING AGENT *

By HERBERT KOTEEN, M.D., F.A.C.P., *New York, N. Y.*

PHYSICIANS and all groups who participate in helping sick people are aware that emotional patterns influence sense of well being and physical health. The success of the witchcraft doctor and the numerous healing cults is in large measure dependent upon the fact that patients achieve a sense of security from discussing their problems with a responsible and sympathetic person, whether he be a recognized physician or simply someone assuming that role. An extensive effort has been made to find therapeutic agents which will relieve emotional tension without impairing intellectual function. The earlier hypnotics, including paraldehyde, chloral hydrate and the bromides, had been used in reduced dosages as sedative agents. Since 1903 the barbiturate acid derivatives have been used extensively. More recently, because antihistaminic agents have been shown to have a mild sedative effect, they too have been exploited as "tranquilizing agents." In 1946 mephenesin was introduced for the purpose of reducing anxiety states and relaxing muscle tension. Although this drug received wide acceptance, subsequent investigation did not support the earlier enthusiasm. In the author's experience, mephenesin has not proved to have therapeutic value and has long since been abandoned.

In April, 1955, two papers appeared describing clinical experiences with an agent similar to mephenesin. These drugs belong to a group known as propanediol derivatives. Berger [1] described a propanediol derivative known as 2-methyl-2-n-propyl-1,3 propanediol dicarbonate. This has been designated as "Miltown." Berger [2] investigated this agent in experimental animals and suggested that Miltown acts as an "interneuron blocking agent" and produces relaxation of skeletal muscles without adversely affecting respiration, or cardiac or other vital functions. Berger [3] and his associates also used Miltown as an anticonvulsive agent in experimental animals and found that the toxicity is low.

In 1955 Selling [4] reported experiences with 187 patients who received between 1,200 and 1,600 mg. (3 to 4 tablets) of Miltown daily. According to the author, all of these patients had regular sessions of psychotherapy in addition to treatment with the drug. The diagnostic labels fixed on these patients by Selling included tension state, anxiety state, alcoholism, behavior

* Received for publication March 6, 1957.

From the Cornell University Medical School and The New York Hospital.

Requests for reprints should be addressed to Herbert Koteen, M.D., 11 East Sixty-eighth Street, New York 21, N. Y.

problems in children, conversion hysteria and involutional depression. A few patients were described as manifesting organic confusion, paranoid psychoses, psychopathic personality and manic depressive psychoses. According to Selling, 158 of the 187 patients improved and only 35 failed to improve. It is stated that within the improved group 64 "recovered completely." Patients were treated for from one to eight months, and the author concluded that Miltown is a practical, safe and clinically useful central nervous system depressant. The author described occasional fainting spells, temperature rises and urticaria in a total of only three patients; an additional five patients experienced gastric discomfort. These were the only toxic manifestations of the drug recorded.

A second clinical report, by Borrus,[5] described the use of Miltown in 104 patients, 67 of whom were classified as anxiety reactions, nine as reactive depressions, and eight as schizophrenic; the remaining patients had a variety of psychiatric diagnoses. Prior to therapy, patients had routine examinations and laboratory studies. The author described the chief side-effect as drowsiness. According to Borrus, of the 104 patients, 24 "recovered completely," 17 had very favorable results, 30 had some favorable effects, and 32 experienced no change.

Both of these authors described gratifying clinical experiences with Miltown, and added that a substantial number of the patients either recovered or improved. In neither report is any reference made to placebo therapy in which neither physician nor patient knew the nature of the agent the patient was receiving. Selling failed to comment further on the possible value of psychiatric therapy, and assumed that the "success" of treatment was related exclusively to the use of the propanediol derivative.

Experimental Studies

In 1954 the author undertook a careful evaluation of the propanediol derivative known as Miltown. The agent was supplied by Dr. Berger, of the Wallace Laboratories, in capsules which were indistinguishable from placebos. Each bottle contained 50 capsules. At no time did the investigator know which product the patient was receiving during the course of the study, because the bottle was handed to the patient and the sealed list containing the key was not available for scrutiny. This method of evaluating therapeutic efficacy of a drug has been described as the "double-blind" technic.

Prior to the distribution of this agent, every patient received a detailed physical examination, including x-ray of the heart and lungs, and routine blood and urine studies. If the patient complained of any symptom which could be ascribed to the new agent, studies were done at once to see if there was any relationship or any fundamental change. When the capsules were distributed each patient was told that he was receiving a new drug which might be of help to him. He was told further that if the agent failed to be of help he would be given a larger dosage the next time.

These patients manifested anxiety, muscle tension, restlessness and irritability. Several had specific muscle groups involved, which included the scaphoid-brachial, the lumbosacral and the anterior cervical groups of muscles. Other patients exhibited muscle tension phenomena extending either unilaterally or bilaterally from the neck area down to the arms. Others complained of tension headaches or abdominal distress under emotional pressures. Two patients in the group were functioning successfully in society despite a schizoid behavior pattern. Two with multiple sclerosis who exhibited hyperreflexia as a manifestation of pyramidal tract disease were given the therapeutic agent to see if it reduced spasticity. One patient who had a postmyocardial infarction shoulder-arm syndrome was not benefited after 30 days of Miltown. He subsequently felt greatly relieved by medication containing salicylic acid, phenacetin and caffeine.

Two patients received as little as 50 capsules of medication, but most had several hundred, and a few had over 500 capsules of either the placebo or

TABLE 1

Evaluation of Effect of Miltown and Placebo on Emotional Tension and Painful Muscle States by the Double-Blind Technic

Agent	No. of Bottles Distributed	Effect of Each Bottle* of Miltown or Placebo	
		Improved	Unimproved
Miltown	37	21	16 (1)†
Placebo	36	23	13 (2)†

* Each bottle contained 50 capsules. Patients took three or four 400 mg. capsules daily.
† Figures in brackets represent number of times patients reported medication caused them to feel worse.

Miltown. Each patient acted as his own control, and detailed notes were taken during each office visit when a new bottle was presented to the patient. The effects of this propanediol derivative, which has been classified as a tranquilizing agent, are summarized in table 1.

At no time was any effort made to persuade the patient that he would be definitely helped by the drug. When a patient returned with an enthusiastic report he was given, without comment, another bottle of medication which appeared indistinguishable to both patient and physician. If the patient expressed the belief that he had not benefited from the previous medication, he was then given another numbered bottle with the suggestion that this contained more of the therapeutic agent. The significant aspect of this technic was that it allowed the patient the privilege of being critical of the medication and *not* of the physician, because he understood that he would be given a more effective capsule on his next visit. This aspect of the study is important, because dependent patients are inclined to report favorably to maintain favor with their physicians. It was recently pointed out [6] that nearly 90% of patients respect and have affection for their personal physicians, but only 62% feel warmth toward the medical profession.

Results

A total of 25 patients participated in this investigation. This represented a distribution of 37 bottles of the presumably effective agent and 36 bottles of the placebo. Each bottle contained 50 capsules; consequently, over 3,600 capsules were distributed. The period evaluated consisted of approximately 1,000 patient days. During the first portion of the experiment the patients were urged to take three capsules daily, each capsule containing 400 mg. of the agent. This is the same amount as is currently distributed in the commercially available Miltown. Subsequently, patients were urged to take four capsules daily, and this was the average dosage maintained for most patients, but in some instances as much as 4,800 mg. were taken daily. The results of the study are summarized in table 1.

Case 1. This patient was a 39 year old woman who was happy and contented until the time of her marriage, which was satisfactory as to her relationship with her husband, but there were religious conflicts, and her first child had a congenital defect and she had been forbidden to have other children. She had also been troubled by parental disapproval of her having married outside of her religion. Because she had identified her father as a superior being, his criticism, although unspoken, was devastating. After her marriage she had exhibited a variety of muscle tension phenomena, including headaches, backaches, and shoulder and arm pains. More recently she had exhibited nausea and vomiting, but repeated investigation of the intestinal tract had been negative. In addition to her muscle tension headaches, she had manifested occasional vascular headaches which had required hospitalization on two occasions. The patient had undergone a year of psychotherapy and had been substantially improved, except for occasional periods of increased tension.

She responded very dramatically to the first bottle of capsules, and described the effects as excellent, with complete reduction in her tension phenomena. Subsequently this bottle was shown to contain Miltown. The second and third bottles were equally effective, and they too contained the therapeutic agent. The fourth bottle the patient found of little value, and this bottle was later found to contain the placebo. The fifth bottle (placebo) the patient considered gave the best results; and she then felt extremely well. Subsequently, the next two bottles (Miltown) failed to help her when she came into conflict with her maid, to whom she felt greatly obligated and whom she feared to discharge. When it was suggested to her that she could run her own household without a maid, she discharged the maid and continued on placebo therapy and continued to feel extremely well. A few weeks later, during a fear of pregnancy, the patient again did poorly. This was later shown to be a time when she was on placebo therapy. When she was assured that the pregnancy did not exist she continued on placebo therapy and felt very well.

Comment: The patient's variation in emotional states was directly influenced by factors other than the medication. Early superficial observation suggested that the medication could have been the significant factor, but close association with the patient and awareness of her environmental threat mechanisms make it apparent in retrospect that the medication was incidental.

Case 2. A 41 year old woman five years earlier had experienced a grippelike syndrome diagnosed as infectious mononucleosis. At that time her physician had told her that she would have muscle pains and joint irritation for many months, and

that she must adapt herself to it. During the ensuing five years the patient complained of constant muscle tensions and joint pains, apparently influenced by the weather. This had obligated the patient, her husband and two children to move to an inland suburb. During these five years the life of the whole family had revolved about the mother's skeletal pains. The patient had been thoroughly investigated by a variety of laboratory procedures in an effort to determine whether she had an obscure collagen disease or was in a rheumatic state. All tests had been negative.

The patient was started on medication and felt dramatically improved on the first bottle (placebo). The second bottle she found of no value, and because there was a different number on the bottle she assumed that this represented a reduced dosage. When she was given a third bottle she was assured that, although the capsule was the same size, it contained a larger quantity of medication, and she promptly felt better. All three bottles proved to contain a placebo. The fourth bottle contained the active agent but caused nausea, increased her body aches and nervousness, and induced insomnia. She felt better on the fifth bottle, which contained Miltown. The sixth bottle made the patient feel much worse, with increase in muscle pains; this bottle contained Miltown. The next bottle was entirely gratifying, and the patient felt improved in all respects; this bottle contained a placebo. The last bottle of the experimental medication that the patient received (Miltown) maintained her improvement, but at this time she had hives and urticaria, and medication was temporarily discontinued. We did not believe the dermatologic reaction was directly related to the medication, so it was decided to learn what could be accomplished by an increased dosage and the patient was given 1,000 tablets of Miltown and was urged to take 12 tablets daily. Although this was not part of the investigation, it was our purpose to determine whether we might obtain any effect from Miltown in a patient who had been previously investigated by the double-blind technic. The patient took 12 tablets for a protracted period, and then was given a second 1,000 tablets. Retrospective analysis of her chart reveals that the patient maintained a state of well being which depended upon environmental factors, and that her periods of satisfactory feelings and periods of depression with muscle tensions bore no fundamental relationship to the medication.

Case 3. A 54 year old engineer had been extremely successful in his profession except that his career had been constantly marred by bouts of alcoholism. He had previously participated in a double-blind investigation of the use of Rauwolfia and Rauwolfia placebos. After he had been firmly convinced that his life was "made over" by the Rauwolfia preparation he was asked to discontinue this tablet and begin on the "Miltown" experiment. He was then given some capsules which he was soon convinced were "worthless." He acknowledged that he resented having been asked to discontinue an effective agent which, at the time, happened to be the Rauwolfia, and to participate in a new investigation. He was a man of superior intelligence and assumed that the capsules were for the purpose of relieving emotional pressure, but was not aware of the placebo or double-blind aspect. He simply assumed that the investigator was comparing the two medications, that is, the Rauwolfia and the new capsule. The patient was actually taking Miltown. He found it very ineffective and gave it to his wife, who found it extremely effective. He then requested a second bottle of medication. This continued to be very helpful for the patient's wife, who had previously been examined and found to be entirely well except for an inactive thyroid nodule. The patient's wife did very well on the second bottle of medication, a placebo. Her tensions and anxieties regarding his alcoholism were minimized.

Case 4. The patient was a 29 year old, exquisitely sensitive, tense, thin, striving young woman who felt completely frustrated in life because of the enormous demands of her parents. They prevented her from having opportunities to meet men and

also demanded a large portion of her salary, which kept her from dressing in a manner she considered satisfactory. She exhibited symptoms suggestive of both hyperthyroidism and pheochromocytoma, but both possibilities were studied with negative results.

The patient was then started on medication (a placebo) and immediately reported that she was less anxious and in better spirits; her appetite was improved, and she said that her friends at work assured her that she was less introspective. On the second bottle (Miltown), she stated that she had more courage and was less nervous. On the third bottle (Miltown) she described herself as feeling "dopey and dragged out." On the fourth bottle (Miltown) she again said that she felt very well and thoroughly secure in her work, and willing to "take on her family and have it out."

Case 5. A patient with tabes dorsalis who was given medication (a placebo) stated that it made her more nervous and irritable, interfered with sleep, and in no way reduced her ataxia or shooting pains. The next bottle (Miltown) caused her to feel exactly the same way. The third bottle (Miltown) made her feel much better, and she was very grateful. The fourth bottle (placebo) gave her headaches and muscle pains, and caused her to be depressed. It is not difficult to interpret this patient's variable reaction states when it is borne in mind that she had intermittent severe shooting pains which would last for a few days and then leave her free of pain for several weeks at a time. However, even when the patient was free of pain she showed anxiety and apprehension as to recurrence of symptoms.

Case 6. A 31 year old woman had exhibited a schizoid behavior pattern in the past but at present was compensated and working reasonably well. Nevertheless, she complained constantly of muscle tension involving the shoulders, arms, forearms, thighs and legs. It was her belief that she had not returned to completely useful function because of these muscle pains, but detailed investigation had failed to reveal any structural cause.

The patient responded dramatically on the first bottle of medication (placebo). The second bottle (Miltown) she said was equally excellent, and the third bottle (placebo) was also thoroughly satisfactory. She then left the city for a few weeks but returned completely disabled; the reason for her disability, she felt, was that she was without this new medication. She was then given six additional bottles of medication, all of which she classified as "good," "excellent" or "marvelous." Three bottles contained Miltown and three contained a placebo, all equally effective.

The two patients with multiple sclerosis failed to respond in any way to Miltown or the placebo. They continued to manifest anxiety, tension and spasticity in gait.

Discussion

It has recently [6] been pointed out how difficult it is to evaluate a new drug properly. Not infrequently, the clinical impression is at variance with conclusions determined by subsequent investigation. This is especially true when the investigator is dependent for his interpretation of the value of the therapeutic agent upon the subjective expression of his patients.

The effect of coincidental environmental circumstances upon the reaction of the patient on drug therapy has been illustrated above. Not uncommonly, both patient and physician are inclined to ascribe changes in the patient's feeling of well-being to the effect of a therapeutic agent rather than to such nonpharmacologic influences as emotional stress, including interfamily relationships, transient and unrelated physical difficulties and, most

important, the fact that the patient is visiting and receiving assurance from a warm and affectionate personality.

Anrep and his associates [7] described the superior therapeutic efficacy of khellin in coronary artery heart disease, and specifically in angina pectoris. They found that the khellin was effective in diminishing or abolishing precordial pain in 90% of 250 patients. Subsequently this therapeutic agent was investigated by Greiner and his associates [8] by the double-blind technic while using a daily report card system. The patients were alternately given khellin and a placebo, and were asked to record the amount of pain for each day of the week. While the patient was receiving the medication neither the patient nor the physician knew whether it was a placebo or the presumed therapeutic agent. The results in 39 patients, involving the comparison of approximately 1,500 days with each of the two agents, showed that khellin had no greater effect than did the lactose placebo in the control of pain of angina of effort.

In 1951 Graham and associates [9] described relief of angina pectoris by intravenous use of heparin. More recently, Engelberg [10] concurred enthusiastically in the value of heparin in the reduction of anginal pain. These authors also felt that the serum lipoproteins were influenced by the use of intravenous heparin. Rinzler and his associates [11] studied the effect of heparin on effort angina of patients with arteriosclerotic heart disease, and compared this effect with that of a placebo by the double-blind method. Heparin was administered to one group of nine patients and a placebo was given concurrently to another nine. These agents were injected intravenously twice weekly over a period of from eight to nine weeks. The results, based on the analysis of almost 2,000 days, revealed that heparin had no greater effect than did the placebo in the control of effort angina. Also, a comparison of the levels of serum lipoproteins showed no significant change in the concentration after six weeks of heparin or placebo administration. Certain side reactions were described by the patients. Dizziness and headaches were more frequently experienced after the placebo than after heparin injection.

The Significance of the Placebo

It is generally understood that the placebo is an inert agent which gives the patient proof that the doctor is interested in him, but which has no pharmacologic action. Often the effect of a new therapeutic agent cannot be convincingly determined until it is matched against a placebo, preferably by the "double-blind" technic. For example, it was presumed for many years that the xanthines and vitamin E were efficacious in relieving anginal pain. When each of these agents was compared by the "double-blind" method to a placebo, it was found that there was no appreciable difference.[12, 13]

In the treatment of a chronic illness in which there are daily variations in the patient's sense of well-being, it is especially difficult to appraise a new

therapeutic agent. It is perhaps for this reason that, about 100 years ago, Trousseau said, "Let's hurry, hurry, use the new drug before it stops curing." Frequently patients are convinced that they have developed a tolerance to a cathartic or an analgesic when, in reality, the placebo effect of the drug is wearing off and the patient feels obliged to "try something new." It must be emphasized that there is nothing inherently wrong in the use of a placebo. Frequently it will establish a good relationship between patient and physician. The problem arises when the doctor believes he is obtaining a desired therapeutic effect through the use of a chemical agent rather than through a psychodynamic approach. Under such circumstances the physician is seriously underestimating the aid to his patients of the impact of his own personality.

Effect of Tranquilizing Agents

The question arises as to whether the new tranquilizing agents are fundamentally different in effect from the barbiturates and comparable sedative agents that have been used for many years. Recently Kolb,[14] in defining the role of psychiatric education in postgraduate training for nonpsychiatrists, stated: "Some may now believe that with the introduction of the tranquilizing agents the anxiety of most patients may be managed capably by the Internist, Neurologist, or Surgeon and that the pressure for instruction in the principles of dynamic psychiatry is lessened. While these drugs significantly alter the quantitative expression of anxiety and panic, they do not modify learned behaviour patterns." It is apparent from this expression that the author believes that there *are* tranquilizing agents, and that these *do* influence the anxieties of patients. Whether there actually are tranquilizing agents remains to be determined, but it appears that the tranquilizing agent that has been used longest, most frequently and most effectively is still the placebo. We may question why this is so. Briefly, it appears to be a fact that the patient is influenced by the dynamic association with the physician, and gains a sense of security from a visit with a compassionate person; the response is directly proportionate to his need for emotional support.

A very significant problem that has resulted from the use of the so-called tranquilizing agents is that they also "tranquilize" the physician. Under the pressure of more patients than he can comfortably handle, the physician is inclined to give each patient some temporizing therapeutic agent which will allow him (the physician) time to think and to investigate the diagnostic problem, and to reduce the pressures imposed by anxious patients. Often he concludes—justifiably or not—that the patient has no structural disease process and must be placated. He consequently makes less effort to understand the psychodynamic factors which make up the patient's personality, and it becomes a matter of expediency to hand the patient a prescription for a simple "tranquilizing agent." The possible harmful effect of this is im-

mediately apparent when it is considered that structural disease processes may be overlooked, and also that the physician, himself "tranquilized," assumes less responsibility for understanding and helping the patient.

Mephenesin (Tolserol, Myanesin) and Meprobamate (Miltown, Equanil)

Mephenesin was first described by Berger and Bradley [15] in 1946. Interest was centered about the presumed muscle-relaxing properties of this agent. This product is similar in chemical structure and pharmacologic action to meprobamate, and both are propanediol derivates. It is prudent to pursue the clinical experience of mephenesin, which has been available as Tolserol and Myanesin.

In 1949 Hay [16] reported that mephenesin reduced agitation in a small series of patients with cerebral vascular disease, as well as in a group of schizophrenics and patients with manic-depressive psychosis. Schlan and Unna [17] described reduction in anxiety symptoms in a group of alcoholics. Dixon et al.[18] believed that this agent allayed symptoms of fear and emotional stress. Comparable reports appeared by Holt,[19] Hecker,[20] Mercer and Hecker,[21] Stungo [22] and Gottesfeld et al.,[23] all finding benefit for patients with various psychiatric disorders.

The clinical reports were accompanied by electroencephalographic data purporting to show that the mephenesin produced changes in the hypothalamus and basal ganglia. Baisset [24] believed that medullary responses were blocked, but Henneman [25] and Kaada [26] suggested that the drug acted on multisynaptic reflexes.

A double-blind controlled study of mephenesin was conducted by Block,[27] who reported that the drug "had little or no long term ameliorative effect." Similarly, Wolf and Pinsky [28] concluded: "The use of placebos to test the effectiveness of mephenesin therapy on certain symptoms resulted in almost the same amount of improvement or lack of it regardless of which the patient was taking." Mendenhall and Ewing,[29] using inert tablets for comparison in a controlled study, found that mephenesin is of little value in alleviating states of anxiety as measured by the Rorschach and Behn tests. In another double-blind study, Hampson et al.[30] observed that "the findings of the present investigation have provided evidence of the efficacy of a placebo and, paradoxically, of the inefficacy of a drug (mephenesin) that has been hailed as therapeutically valuable."

The initial reports about this second propanediol derivative, meprobamate (Miltown, Equanil), described it as having unusual value for numerous emotional disturbances. It will be interesting to observe subsequent clinical appraisals.

Summary and Conclusions

1. The effect of a new therapeutic agent, a member of the propanediol group known as Miltown, has been investigated. This product is identical

to Equanil, which is marketed under a different trade name but is chemically the same. Both products are referred to as "tranquilizing agents" and are produced as 400 mg. tablets.

2. The effect of Miltown on emotional tension and muscle discomfort was compared with that of a matching placebo by the "double-blind" method. By this technic, neither patient nor physician knows whether the medication dispensed is the active or the inert material.

3. Miltown and placebo were dispensed in capsules to a total of 25 patients, who took approximately 3,600 capsules for a total of 1,000 patient days. All patients took between 1,200 and 1,600 mg. daily, the currently recommended dose.

4. The results reveal that Miltown in this dosage had no greater effect in relieving symptoms than did the placebo in this group of unselected patients. The effects of larger dosage on the central nervous system were not explored.

5. There is some danger that, after prescribing a so-called "tranquilizing agent," the physician may lose interest in the basic problems of his patient.

ACKNOWLEDGMENT

Miltown capsules and placebo capsules were supplied by Dr. F. M. Berger, of the Wallace Laboratories, New Brunswick, New Jersey.

SUMMARIO IN INTERLINGUA

Es constantemente offerite nove drogas con varie pretentiones therapeutic. In multe casos, il es difficile evalutar le meritos de tal nove agentes, specialmente quando illos es destinate a tractar o a beneficiar patientes con symptomatologias non-specific. Un del melior methodos pro le evalutation de nove agentes de iste genere es le technica "bis-occulte." In illo, ni le patiente ni le medico sape durante le integre curso del experimento qual medication—le agente a testar o un substantia cognoscitemente inerte—es administrate. Per consequente, quando le patiente reporta su observationes, le medico es restringite a notar los, e il es solmente post le termination del experimento que le medico apprende si le responsas describite per le patiente occurreva post administrationes del agente in question o subsequente al uso del substantia inerte.

Ha essite investigate le effectos de un nove "agente therapeutic" que es un membro del gruppo de propanediol cognoscite como "Miltown." Iste producto es identic a "Equanil." Ambes es describite como "agentes tranquillisante" e es producite in le forma de tablettas de 400 mg. Le grande majoritate del patientes qui prende iste agentes al tempore presente recipe inter tres e quatro tablettas per die, i.e. inter 1.200 e 1.600 mg.

Le effecto de Miltown super tension emotional e disconforto muscular esseva comparate per medio del methodo "bis-occulte" con le effecto de un medication fictitie de apparentia non distinguibile. Nunquam durante le curso del experimento sapeva le autor qual producto le patiente habeva recipite quando ille describeva le effectos attribuite a illo. Miltown e le medication fictitie esseva administrate in capsulas del mesme forma e color a 25 patientes. Esseva usate un total de circa 3.600 capsulas, lo que corresponde a plus o minus 1.000 dies-patiente. Omne le patientes recipeva inter 1.200 e 1.600 mg per die, i.e. le dose que es currentemente recommendate. Le resultatos monstrava que in iste dosage e in iste gruppo de non-seligite patientes con varie gravamines, le alleviamento del symptomas effectuate per Miltown non esseva plus grande que illo effectuate per le medication fictitie. Le

effecto de plus grande doses super le systema nervose central non esseva explorate. Il existe le periculo que post prescriber le si-appellate "agentes tranquillisante," le medicos perde lor interesse in le problema fundamental de lor patientes proque illes ha satisfacite lor deber de "occupar se" del patientes e lor gravamines. Sub iste conditiones un hiato es un occurrentia frequente in le relationes inter le patiente e le medico.

BIBLIOGRAPHY

1. Berger, F. M.: The pharmacologic properties of 2-methyl-n-propyl-1,3-propanediol dicarbonate (Miltown), J. Pharmacol. and Exper. Therap. **112**: 413, 1954.
2. Hendley, C. D., Lynes, T. E., and Berger, F. M.: Effect of 2-methyl-n-propy-1,3-propanediol dicarbonate on the central nervous system, Proc. Soc. Exper. Biol. and Med. **87**: 608, 1954.
3. Berger, F. M., and Ludwig, B. J.: The anticonvulsant action of 2,2-diethyl-1,3-propanediol and some of its homologues and esters, J. Pharmacol. and Exper. Therap. **100**: 25, 1950.
4. Selling, L. S.: Clinical study of a new tranquilizing drug (Miltown), J.A.M.A. **157**: 1594, 1955.
5. Borrus, J. C.: Study of effect of Miltown on psychiatric states, J. A. M. A. **157**: 1596, 1955.
6. Editorial, New England J. Med. **254**: 484, 1956.
7. Anrep, G. V., Kenway, M. R., and Barsoum, G. S.: The coronary vasodilator action of khellin, Am. Heart J. **37**: 531, 1949.
8. Greiner, T., Gold, H., Cattell, M., Travell, J., Bakst, H., Rinzler, S. H., Benjamin, Z. H., Warshaw, L. J. Bobb, A. L., Kwit, N. T., Modell, W., Rothendler, H. H., Messeloff, C. R., and Kramer, M. L.: A method for evaluation of the effects of drugs on cardiac pain in patients with angina of effort, Am. J. Med. **9**: 143, 1950.
9. Graham, D. M., Lyon, T. P., Gofman, J. W., Jones, H. B., Yankley, A., Simonton, J., and White, S.: Blood lipids and human atherosclerosis. The influence of heparin upon lipoprotein metabolism, Circulation **4**: 666, 1951.
10. Engelberg, H.: Heparin therapy of severe coronary atherosclerosis with observations of its effect on angina pectoris, Am. J. M. Sc. **224**: 487, 1952.
11. Rinzler, S. H., Travell, J., Bakst, H., Benjamin, Z. H., Rosenthal, R. L., Rosenfield, S., and Hirsch, B. B.: Effect of heparin in effort angina, Am. J. Med. **14**: 438, 1953.
12. Gold, H., Kwit, N. T., and Otto, H.: The xanthines in the treatment of cardiac pain, J. A. M. A. **108**: 2173, 1937.
13. Travell, J., et al.: Comparison of effects of alpha-tocopherol with a matching placebo on chest pains in patients with heart disease, Ann. New York Acad. Sc. **52**: 345, 1949.
14. Kolb, L. C.: The psychiatric viewpoint in training residents, J. A. M. A. **161**: 21, 1956.
15. Berger, F. M., and Bradley, W.: The pharmacological properties of alpha: beta-dihydroxy-v-(2 methylphenoxy)-propane (Myanesin), Brit. J. Pharmacol. **1**: 266, 1946.
16. Hay, J.: Observations on the use of Myanesin in psychiatric cases, Canad. M. A. J. **60**: 225, 1949.
17. Schlan, L. S., and Unna, K. R.: Some effects of Myanesin in psychiatric patients, J. A. M. A. **140**: 672, 1949.
18. Dixon, H. H., Dickel, H. A., Coen, R. A., and Haugen, G. B.: Clinical observations on Tolserol in handling anxiety tension states, Am. J. M. Sc. **220**: 23, 1950.
19. Holt, W. L., and Borkowski, W.: The value of drugs that raise seizure threshold in therapeutic electric brain stimulation, J. Nerv. and Ment. Dis. **114**: 177, 1951.
20. Hecker, A. O., Mercer, M., and Griffin, M. A., Jr.: Further clinical investigation of Tolserol (Myanesin), Dis. Nerv. System **12**: 99, 1951.
21. Mercer, M., and Hecker, A. O.: The use of Tolserol (Myanesin) in psychological testing, J. Clin. Psychol. **7**: 263, 1951.

22. Stungo, E.: Mephenesin in psychiatric conditions (Letter), Lancet **2**: 931, 1950.
23. Gottesfeld, B. H., Mann, N., and Conway, E.: The role of the internist in the treatment of alcoholism, Connecticut M. J. **15**: 678, 1951.
24. Baisset, A., Laporte, Y., and Grezes-Rueff, F.: Effect of alpha: beta-dihydroxy-v-(2 methylphenoxy)-propane on medullary synaptic transmission in the acute spinal dog, Compt. rend. Soc. de biol. **143**: 1515, 1949.
25. Henneman, E., and Scherrer, J.: Mode of action of Myanesin on central nervous system, Tr. Am. Neurol. A. **74**: 208, 1949.
26. Kaada, B. R.: Site of action of Myanesin (mephenesin, Tolserol) in the nervous system, J. Neurophysiol. **13**: 89, 1950.
27. Block, S. L.: Effect of mephenesin upon anxiety, Arch. Neurol. and Psychiat. **69**: 727, 1953.
28. Wolf, S., and Pinsky, R. H.: Effects of placebo administration and occurrence of toxic reactions, J. A. M. A. **155**: 339, 1954.
29. Mendenhall, J. H., and Ewing, J. A.: Further psychometric evaluation of the effect of mephenesin on anxiety, J. Ment. Sc. **100**: 262, 1954.
30. Hampson, J. L., Rosenthal, D., and Frank, J. D.: A comparative study of the effect of mephenesin and placebo on the symptomatology of a mixed group of psychiatric outpatients, Bull. Johns Hopkins Hosp. **95**: 170, 1954.

CASE REPORTS

CRYPTOCOCCUS RENAL INFECTION: REPORT OF A CASE*

By Alfred P. Spivack, M.D., Jay A. Nadel, M.D., and George M. Eisenberg, D.Sc., *Philadelphia, Pennsylvania*

Since Zenker first reported a case of cryptococcal infection of man in 1861,[23] review articles have shown an increasing number of reported cases.[15, 16, 19] This is most probably due to a greater awareness of the disease and to improved laboratory diagnostic procedures. *Cryptococcus neoformans* is a yeastlike, nonsporulating, budding fungus characterized by the development of a wide capsule both in tissue and in culture. It is ovoid to spherical in shape, and 5 to 15 μ in diameter.[11] The organism and its characteristic capsule can be demonstrated both in culture on Sabouraud's glucose medium and directly in spinal fluid by emulsifying the specimen with India ink on a microscope slide.

Infection produced by this fungus is most commonly associated with central nervous system involvement. While localized infections do occur,[18] and involvement of the kidney is not uncommon in systemic cryptococcosis, the case reported here is unusual in the finding of the organisms apparently confined to the kidney and perirenal tissue. Review of the literature has failed to reveal a previous report of a similar case.

Case Report

The patient was born in North Carolina on November 21, 1928, and had lived there as a farmer prior to coming to Philadelphia. Although he had been rejected for military service in North Carolina in 1950 (for reasons which could not be determined), he stated that his chest x-ray, done on routine survey, had been reported as normal in 1949.

In November, 1951, he was referred to a Philadelphia chest clinic because of an abnormal survey chest x-ray. At this time chest x-ray and lymph node biopsy findings were compatible with a diagnosis of Boeck's sarcoid. The tuberculin skin test was negative. In September, 1952, a chest x-ray indicated progression of the disease, and after a 28 day trial of cortisone there was thought to be an increase in the abnormal pulmonary shadows. No other studies were reported during this time.

No medical record is available from this time until the patient was admitted to Philadelphia General Hospital on October 8, 1954, with symptoms suggestive of a right-sided pyelonephritis, intermittently present for three months prior to admission. He was found to be a well developed Negro male; pulse, 72; blood pressure, 115/65 mm. of Hg; temperature, 98.6° F. Ophthalmologic examination revealed bilateral corneal opacities, a normal fundus, and posterior synechiae of the iris of both eyes, thought to be due to an old uveitis. When questioned, he stated that he had had

* Received for publication December 22, 1955.

From the Departments of Medicine and Laboratories, Philadelphia General Hospital (Blockley Division), Philadelphia, Pennsylvania.

Requests for reprints should be addressed to Alfred P. Spivack, M.D., Philadelphia General Hospital, Philadelphia 4, Pennsylvania.

bilateral "conjunctivitis" in 1950. There was tenderness in the right upper quadrant and right costovertebral angle, in addition to generalized small palpable lymph nodes.

Urinalysis on admission showed 30 to 40 white blood cells, 0 to 5 red blood cells per high power field, and a specific gravity of 1.016. Bacteriologic examination of the urine revealed the presence of alpha hemolytic enterococcus, Paracolobactrum sp., and *Proteus mirabilis*. Hematologic examination revealed a hemoglobin of 10.5 gm. per 100 c.c., with slightly hypochromic erythrocytes. Leukocyte count was 10,700 per cubic millimeter (neutrophils, 83%; lymphocytes, 11%; monocytes, 4%; eosino-

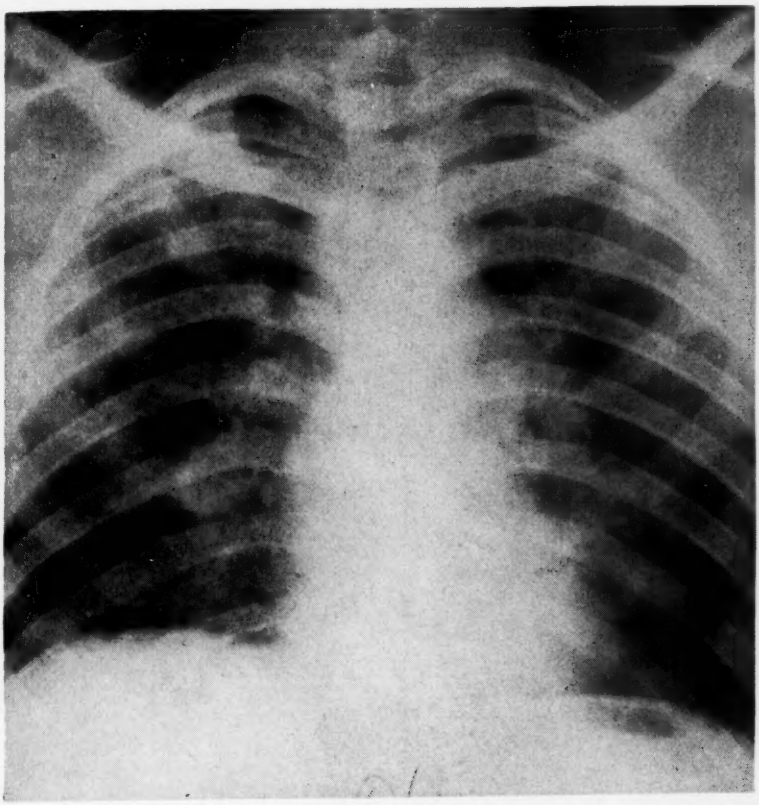


FIG. 1. Chest x-ray, October 11, 1954, showing miliary infiltration throughout both lung fields and bilateral hilar adenopathy.

phils, 2%). The following blood chemical studies revealed normal values: fasting blood sugar, blood urea nitrogen, calcium, phosphate, acid and alkaline phosphatase, proteins, cephalin and thymol flocculation, bromsulphalein excretion, and cholesterol. Tests for syphilis and for the presence of antibodies indicative of infections due to typhoid, paratyphoid and *Brucella abortus* were negative, as was the Weil-Felix test.

Numerous examinations, both smear and culture, of the patient's urine, sputum and gastric contents failed to reveal acid-fast bacilli, and the tuberculin test was again negative. Chest x-ray (figure 1) showed miliary infiltration throughout both lung

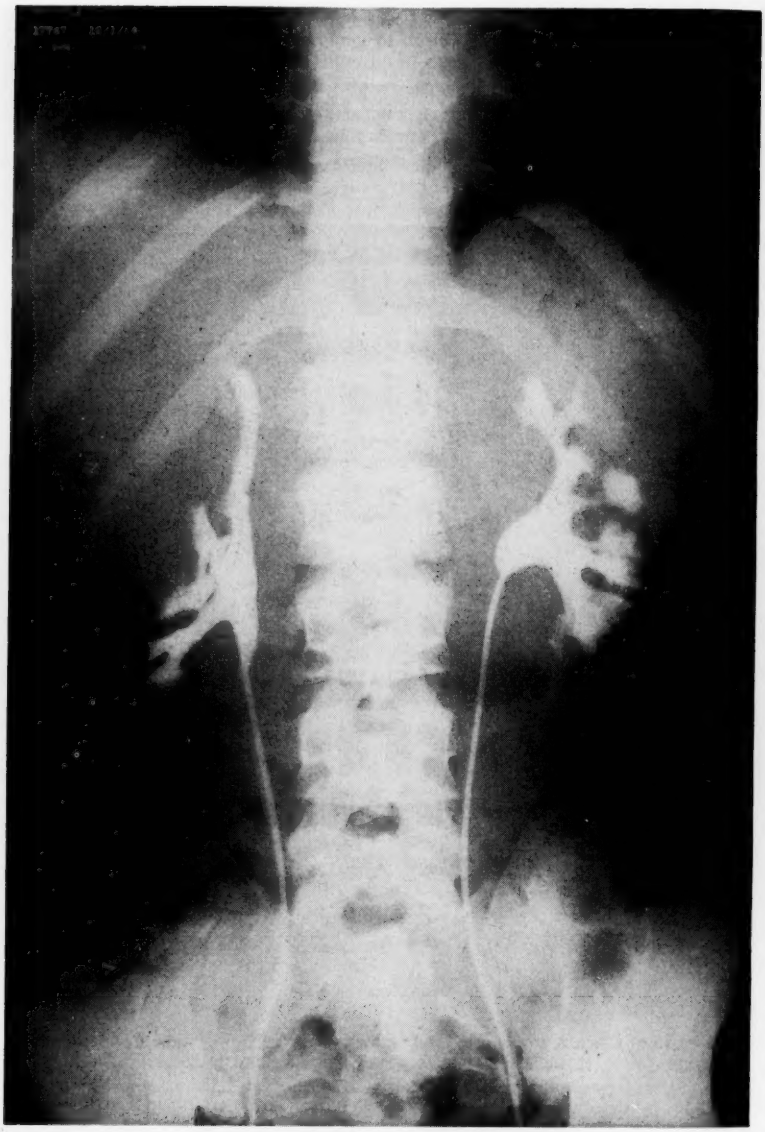


FIG. 2. Retrograde pyelogram, December 1, 1954, showing elongation and compression of the upper and middle calyces of the right kidney.

fields and bilateral hilar adenopathy. X-rays of the hands, feet and skull were normal. A lymph node biopsy was reported as compatible with either tuberculosis or Boeck's sarcoid. On intravenous pyelography, elongation and compression of the upper and middle calyces of the right kidney were found, with similar findings on

retrograde pyelography (figure 2). Retroperitoneal air study (figure 3) showed an incomplete outline of the outer margin of the upper pole of the right kidney, suggesting a mass lesion.

On December 1, 1954, a right nephrectomy was performed and the kidney was found to be adherent to the surrounding structures, making exposure and removal extremely difficult. The specimen had considerable purulent drainage and consisted of kidney and perirenal tissue approximately 8 by 5 by 4 cm., the upper half of which was a shaggy mass of firm, reddish brown and pink perirenal tissue firmly adherent to the renal surface. Underlying the perirenal tissue and involving the central upper portion of the renal pelvis and calyces was a firm, nodular mass which appeared only partially encapsulated. There were similar very small lesions involving the minor calyces of the opposite pole. Histologic examination of the kidney revealed

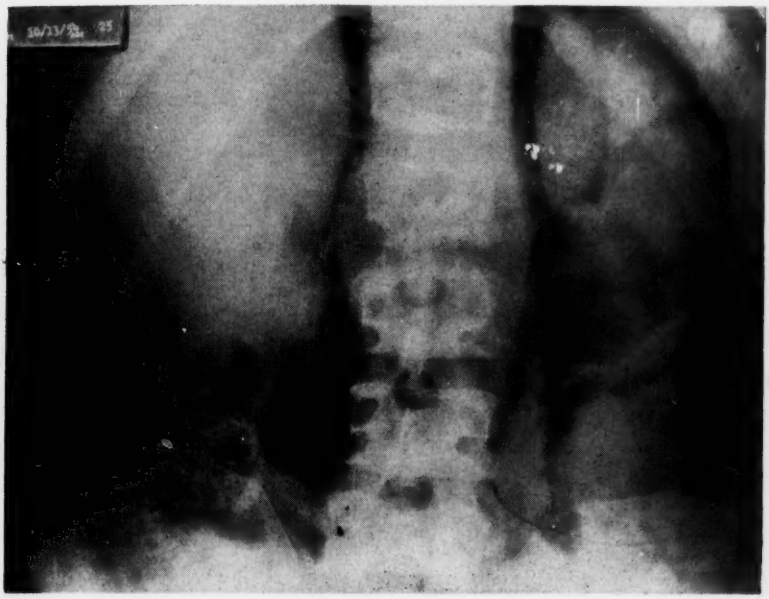


FIG. 3. Retroperitoneal air study, October 13, 1954, showing incomplete outline of the upper pole of the right kidney.

the presence of granulomatous lesions in the cortex separated by dense, collagenous connective tissue (figure 4). The granulomas consisted of macrophages and plasma cells, with polymorphonuclear leukocytes in the center. Yeastlike organisms, later identified as *C. neoformans,* were also found both outside and within the macrophages (figure 5).

Postoperatively the patient continued to drain large amounts of greenish gray, foul-smelling pus from the nephrectomy site, and although fungus cultures of the kidney itself were not done, direct microscopic examination and culture of the pus revealed organisms morphologically consistent with cryptococcus. Histoplasmin, blastomycin, coccidioidin and torulin skin tests postoperatively were negative. The methylene blue dye absorption test for toxoplasmosis * was reported as positive in a

* Performed by the Laboratory of Tropical Diseases, National Microbiological Institute, National Institutes of Health, Bethesda, Maryland.

FIG. 4. Granulomatous lesions in the cortex of the kidney, H. & E. ×29.

FIG. 4. Granulomatous lesions in the cortex of the kidney, H. & E. × 29.

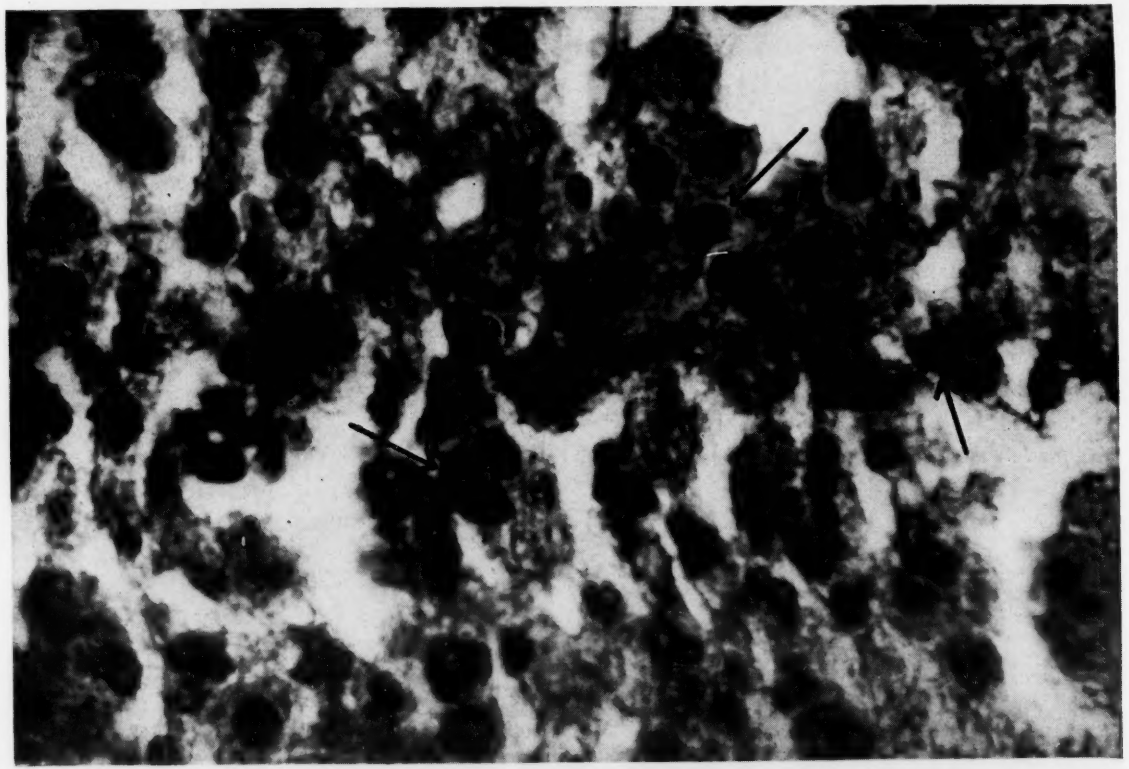


FIG. 5. *Cryptococcus neoformans* within one of the renal foci of granulomatous inflammation, Ritter-Oleson stain. × 1,350.

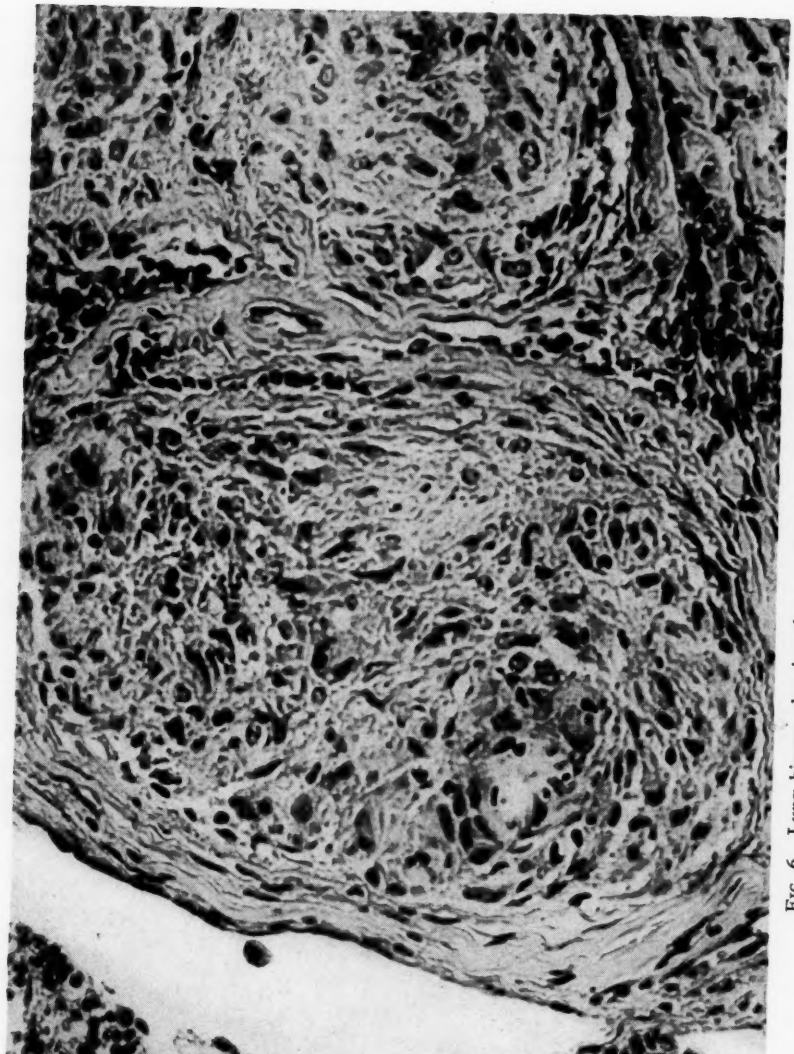


FIG. 6. Lung biopsy, showing the granulomatous reaction, H. & E. × 184.

serum dilution of only 1 to 16; complement fixation tests for histoplasmosis † were negative. Spinal fluid examination for cells, protein, chlorides and sugar yielded normal findings; serologic tests for syphilis and colloidal gold were negative at the same time. Bone marrow examination was normal except for mild hypoplasia of the hematopoietic tissue. Cultures for bacteria, fungi and acid-fast bacilli of bone marrow and spinal fluid showed no growth; examination of sputum, urine and feces at this time failed to reveal fungi morphologically resembling cryptococcus. Stool specimens contained no ova or parasites.

On January 6, 1955, lung biopsy revealed multiple confluent nodules of epithelioid cells and giant cells compatible with a diagnosis of Boeck's sarcoid (figure 6). No yeastlike organisms were seen in the sections, and none were recovered in culture or by animal inoculation. Shortly after this, adrenal function was evaluated and found to be within the lower limits of normal on intravenous insulin tolerance test, 48 hour ACTH test of 17-ketosteroid excretion, A value and Thorn test.

On January 23, 1955, a fistulous tract between the second part of the duodenum and the draining nephrectomy wound was demonstrated by x-ray and contrast media. On February 17, 1955, the nephrectomy scar was incised and a retroperitoneal abscess cavity with numerous fistulous tracts was converted into one large open defect. There was gradual closure during the next two months, and on April 14, 1955, a small fistula from the hepatic flexure of his large intestine was found. The patient has been followed in the outpatient clinic and, when seen in October, 1955, was asymptomatic, with no residual x-ray evidence of fistulae.

Microbiologic Aspects

Identification of the organism as a member of the genus Cryptococcus was established presumptively on the basis of the following criteria: a yeastlike fungus producing an easily recognizable, gelatinous capsule associated with a mucous type of growth and failure to produce true mycelium and ascospores. Species differentiation between the pathogenic *Cryptococcus neoformans* and the nonpathogenic *Cryptococcus neoformans* var. *innocuous* was based on Benham's criteria.[4] These include the ability to grow at 37° C., and to assimilate dextrose, maltose, sucrose and galactose; and the failure to assimilate lactose or potassium nitrate as determined by auxanographic technics. Final demonstration of virulence was made by intracerebral inoculation of white mice, in which at autopsy large numbers of morphologically typical cryptococci were visualized microscopically in fresh preparations of the brain, liver, heart and kidney. Cultures from these organs also yielded typical cryptococcal colonies. Organisms were also found in histologic sections of these organs; figure 7 illustrates the findings in the lung.

Discussion

In a search for another pathogenic fungus in soil, Emmons [12] noted the incidental finding of *Cryptococcus neoformans*. This was the first direct evidence that the organism was present in soil, and, although it was not demonstrated in air, he felt that the type of thick encapsulation found in culture would be sufficiently resistant to drying to enable the organism to survive and become disseminated in air from a source in soil. To our knowledge there are no recorded cases of transmission from man to man, or from animal to man; but in view of

† Performed by the General Diagnostic Laboratory Communicable Disease Center, Public Health Service, Chamblee, Georgia.

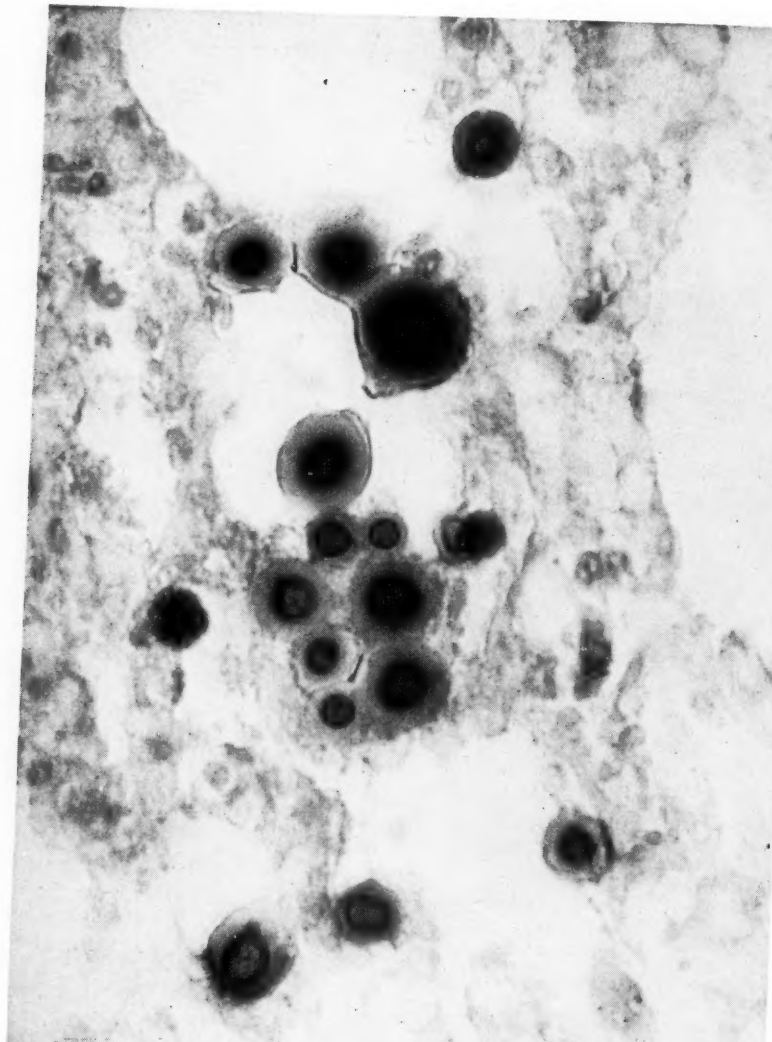


FIG. 7. *Cryptococcus neoformans* within the mouse lung, Ritter-Oleson stain. × 828.

the fact that several cases of pulmonary cryptococcus infection are known to have healed with or without evidence of scarring, it is possible that the lung may be the primary site from which the organisms become disseminated.[5, 14] Others have mentioned the prostate [6, 22] or skin [17] as a possible site of primary infection. Wade and Stevenson [20] inoculated mice intracerebrally, intravenously, intraperitoneally, subcutaneously and intratracheally and could not produce central nervous system involvement without visceral involvement, chiefly of the lung and kidney and, less frequently, of the liver and spleen. This they have taken to indicate a true septicemia.

In a report of 172 cases,[16] the central nervous system was found to be the only site of involvement in about 50%. Of the tissues involved in addition to the central nervous system, the lungs were involved in about one fourth of the cases, the kidneys in about one eighth, and the spleen, adrenal, peribronchial lymph nodes, skin and subcutaneous tissue to a lesser extent. In nearly 20% of recorded cases, enlarged lymph nodes are mentioned, at times with a histologic picture suggestive of Boeck's sarcoid.[17] In addition to this, an increased incidence of cryptococcosis has been found in patients with malignant diseases of the reticuloendothelial system.[24] Various reports have shown involvement of almost every organ, which again is suggestive of a septicemic phase.

It is interesting to note that in the case presented in this paper the patient had been told that his chest x-ray was normal in 1949, but in 1950 he was rejected for military service (for reasons which could not be determined). At about this same time he developed his ocular infection, and a year later he was diagnosed as having Boeck's sarcoid. Although the lung biopsy was reported as compatible with a diagnosis of Boeck's sarcoid, and the uveitis is not uncommonly seen with this latter disease, it is interesting to speculate on their possible cryptococcal etiology.

A variety of ophthalmologic manifestations is frequently observed during the course of cryptococcal meningo-encephalitis, and two cases of cryptococcal chorioretinitis have been reported in which no other site of infection by this fungus could be demonstrated.[10] Wager [21] has reported a case of cryptococcal uveitis in a patient who died of central nervous system involvement.

The pulmonary lesions of this fungus disease have been studied by Haugen and Baker,[14] whose findings were: (a) subpleural nodules less than 1.5 cm. in diameter, predominantly nonencapsulated conglomerations of giant cells, lymphocytes, macrophages, occasional "caseous necrosis" and fibrous tissue with numerous organisms and with no calcification or involvement of hilar nodes analogous to the primary complex of tuberculosis; (b) larger pulmonary nodules, of 3.5 to 7.5 cm.; and (c) miliary pulmonary lesions consisting of gelatinous masses of organisms. There were no large lobar lesions or cavities in this series. In a later report [1] on the tissue pathology of 26 autopsies of systemic cryptococcosis, these same authors found a correlation between the duration of the disease and the tissue changes. The early lesions were gelatinous and consisted of masses of organisms with little inflammatory response, while the older lesions were granulomatous. "Caseous necrosis" was found to be an unusual tissue response, and consisted of necrotic masses of organisms, in contrast to the caseation of tuberculosis, which consists of necrotic reactive cells of the body. Voyles and Beck [19] previously had reported the yeast cells to be ill defined in the older lesions.

In view of these findings, it is possible that the change in radiologic appearance

of the chest and the ocular infection of the case presented in this report might have represented the initial infection and hematogenous dissemination of *Cryptococcus neoformans,* the renal infection being a more recent or more resistant site of secondary infection. As has been stated before, renal lesions are not uncommon in systemic cryptococcosis, and yeast cells have been seen in the glomeruli [19] and in the granulomatous infiltrations of the kidney.[19, 22] A case of central nervous system involvement has been recorded in which there was an area of granulomatous change in one kidney where no organisms were found.[13]

Cutaneous hypersensitivity to *Cryptococcus neoformans* is not common, and circulating antibodies to the latter are similarly not demonstrable in the majority of human sera from active cases.[2] It is therefore not unusual that the torulin skin test should have been negative in the case presented in this report.

No specific therapy exists for cryptococcosis,[7, 9, 15] but on the basis of laboratory studies [8] a combination of cycloheximide (Acti-dione) and polymyxin B has been recommended where there is central nervous system involvement. Polymyxin is fungicidal for *Cryptococcus neoformans,* whereas cycloheximide, which has been used in human cases,[7, 9] is fungistatic. In dual combination they appear to show potentiation of action in animal studies, without the development of resistance.[8] Spontaneous clinical remissions are known to occur, and a case of cryptococcal meningitis of nearly 16 years' duration has been reported.[3] Caution should therefore be exercised in evaluating reports of therapy.

Summary

A case is presented of renal infection due to *Cryptococcus neoformans* var. *hominis* in a patient in whom the pulmonary findings were compatible with Boeck's sarcoid.

Acknowledgments

The authors wish to thank Miss J. M. O'Loughlin for performing the mycologic studies, Mrs. Helen Boyle for preparing the histologic sections and Miss Maureen Mallin for her assistance in preparing the manuscript.

Summario in Interlingua

Es presentate un caso de infection renal causate per *Cryptococcus neoformans* var. *hominis* in un patiente in qui le constatationes pulmonar esseva compatibile con sarcoide de Boeck. Le patiente, un masculo negre, habeva nascite in Nord-Carolina in 1928 ubi ille habeva residite como agricultor usque a su venir a Philadelphia in 1951. In 1952, un diagnose de sarcoide de Boeck esseva facite pro ille, e post un curso tentative de 28 dies de cortisona il pareva que le anormal umbras pulmonar se augmentava.

Le patiente se representava in 1954 con symptomas de pyelonephritis al latere dextere. Roentgenogrammas con substantia de contrasto revelava un lesion in le forma de un massa al polo superior del ren dextere. Esseva etiam constatate bilateral opacitates corneal e synechias posterior del irides in ambe oculos. Nephrectomia esseva effectuate, e le examine histologic del ren revelava le presentia de lesiones granulomatose in le cortice que contineva organismos saccharomycoide identificate como *Cryptococcus neoformans.*

Post le operation le patiente continuava drainar grande quantitates de pus malodor ab le sito del nephrectomia. Esseva demonstrate connexiones fistulose inter le secunde parte del duodeno e le vulnere nephrectomic que esseva le sito del drainage de pus. Iste connexiones esseva transformate chirurgicamente in un grande defecto

aperte que se claudeva gradualmente in le curso del sequente duo menses. Un anno post su hospitalisation le patiente esseva asymptomatic. Radiogrammas exhibiva nulle evidentia residue de fistulas.

Infectiones producite per le fungo *Cryptococcus neoformans* es associate le plus communmente con affectiones del systema nervose central. Durante que infectiones localisate occurre e ben que affectiones renal non es incommun in cryptococcosis systemic, le caso hic reportate es inusual per le constatation que le organismo esseva apparentemente restringite al histos renal e perirenal. Un examine del litteratura ha revelate nulle previe reporto de un caso de iste genere.

BIBLIOGRAPHY

1. Baker, R. D., and Haugen, R. K.: Tissue changes and tissue diagnosis in cryptococcosis (a study of twenty-six cases), Am. J. Clin. Path. **25**: 14–24, 1955.
2. Beamer, P. R.: Immunology of mycotic infections, Am. J. Clin. Path. **25**: 66–75, 1955.
3. Beeson, P. B.: Cryptococcic meningitis of nearly sixteen years' duration, Arch. Int. Med. **89**: 797–801, 1952.
4. Benham, R. W.: The genus Cryptococcus: the present status and criteria for the identification of species, Tr. New York Acad. Sc. **17**: 418–429, 1955.
5. Bowman, H. E., and Ritchey, J. O.: Cryptococcosis (torulosis) involving the brain, adrenal, and prostate, J. Urol. **71**: 373–378, 1954.
6. Cohen, J. R., and Kaufmann, W.: Systemic cryptococcosis: a report of a case with review of the literature, Am. J. Clin. Path. **22**: 1069–1076, 1952.
7. Carton, C. A.: Treatment of central nervous system cryptococcosis: a review and report of four cases treated with Acti-dione, Ann. Int. Med. **37**: 123–154, 1952.
8. Carton, C. A., and Liebig, C. S.: Treatment of central nervous system cryptococcosis; laboratory studies, Arch. Int. Med. **91**: 773–783, 1953.
9. Carton, C. A., and Mount, L. A.: Neurosurgical aspects of cryptococcosis, J. Neurosurg. **8**: 143–156, 1951.
10. DeBuen, S., Zimmerman, L. E., and Foerster, H. C.: Patologia ocular en la criptococosis, Rev. d. Inst. salub. y enferm. trop. **14**: 163–178, 1954.
11. Dubos, R. J.: *Cryptococcus neoformans, in* Bacterial and mycotic infections of man, 2nd Ed., 1952, J. B. Lippincott & Co., Philadelphia, pp. 657–661.
12. Emmons, C. W.: Isolation of *Cryptococcus neoformans* from soil, J. Bact. **62**: 685–690, 1951.
13. Halpert, B., Whitcomb, F. C., McRoberts, C. C., and Carton, C. A.: Systemic and central nervous systemic involvement in cryptococcosis and coccidioidomycosis, South. M. J. **47**: 633–642, 1954.
14. Haugen, R. K., and Baker, R. D.: The pulmonary lesions in cryptococcosis with special reference to subpleural nodules, Am. J. Clin. Path. **24**: 1381–1390, 1954.
15. Levin, E. A.: Torula infection of the central nervous system, Arch. Int. Med. **59**: 667–684, 1937.
16. Mosberg, W. J., Jr., and Arnold, J. G., Jr.: Torulosis of the central nervous system: review of the literature and report of five cases, Ann. Int. Med. **32**: 1153–1183, 1950.
17. Nichols, D. R., and Martin, W. J.: Cryptococcosis: clinical features and differential diagnosis, Ann. Int. Med. **43**: 767–780, 1955.
18. Ratcliffe, H. E., and Cook, W. R.: Cryptococcosis; review of the literature and report of a case with initial pulmonary findings, U. S. Armed Forces M. J. **1**: 957–969, 1950.
19. Voyles, G. Q., and Beck, E. M.: Systemic infection due to *Torula histolytica* (*Cryptococcus hominis*). I. Report of four cases and review of the literature, Arch. Int. Med. **77**: 504–515, 1946.
20. Wade, L. J., and Stevenson, L. D.: Torula infection, Yale J. Biol. and Med. **13**: 467–476, 1941.

21. Wager, J. E., and Calhoun, F. P., Jr.: Torula uveitis, Tr. Am. Acad. Ophth. **58**: 61–67, 1954.
22. Zelman, S., O'Neil, R. H., and Plaut, A.: Disseminated visceral torulosis without nervous system involvement; with clinical appearance of granulocytic leukemia, Am. J. Med. **11**: 658–664, 1951.
23. Zenker, F. A.: Encephalitis mit Pilzentwicklung im Gehirn, Jahresb. d. Gesellsch. f. Natur- und Heilk. in Dresden, 1861–1862, pp. 51–52.
24. Zimmerman, L. E., and Rappaport, H.: Occurrence of cryptococcosis in patients with malignant disease of reticuloendothelial system, Am. J. Clin. Path. **24**: 1050–1072, 1954.

AUTO-IMMUNE HEMOLYTIC ANEMIA ARRESTED BY REMOVAL OF AN OVARIAN TERATOMA: REVIEW OF THE LITERATURE AND REPORT OF A CASE *

By KEVIN G. BARRY, Major (MC) USA, *Governors Island, New York,* and WILLIAM H. CROSBY, Lt. Colonel (MC) USA, *Washington, D. C.*

THE separation of specific diseases from an amorphous mother group is a measure of medical progress. The purpose of the present report is to focus attention on one such specific entity in the hope that it may be diagnosed more frequently, inasmuch as it is one form of auto-immune hemolytic anemia (AHA) that is readily curable.[1, 3, 4, 6]

The mechanism of auto-immune hemolytic disease remains as elusive as ever.[10, 11] In some cases, such as this one, the formation of antibodies against the patient's own red cells appears to be related somehow to the presence of a neoplasm.[1, 9] In the majority of cases the neoplasm is malignant,[12] and if the patient does not die of hemolytic anemia he dies eventually of the primary disease. Other forms of this so-called symptomatic auto-immune hemolytic anemia are those associated with syphilis (paroxysmal cold hemoglobinuria), virus pneumonia, infectious mononucleosis, pregnancy, sarcoidosis and Felty's syndrome.[10] In general, these conditions are self-limited or yield to treatment and the hemolytic anemia disappears. When auto-immune hemolytic anemia is associated with an ovarian teratoma it may remain active and destructive for years, but it is cured completely by removal of the tumor. In a discouragingly large proportion of the reported cases the teratoma was discovered too late [5, 7, 8] (table 1). Even though this is a rare disease one should, because of the possibility of cure, keep the dermoid in mind when confronted with a case of autohemolytic anemia.

CASE REPORT

The patient, a 26 year old married Negro female nurse, presented herself at Walter Reed Army Hospital in January, 1955, requesting transfusion for severe sickle cell anemia.

* Received for publication December 6, 1955.
From the Hematology Service, Walter Reed Army Hospital, and the Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C.
Requests for reprints should be addressed to William H. Crosby, Lt. Colonel (MC), Department of Hematology, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington 12, D. C.

TABLE 1

Data from Case Reports of Auto-Immune Hemolytic Anemia Associated with Teratomata

Author	Age in Years 1	Duration of Illness 2	Splenomegaly 3	Palpable Tumor 4	Hemoglobin, gm. % 5	Spherocytosis 6	Reticulocytes, % 7	Bilirubinemia 8	In Vitro Antibodies Found 9	Outcome
1. West-Watson and Young, 1938	44	2 mo.	×	+	3.6	+	45.5	+	+	Splenectomy without remission. Dramatic complete clinical recovery after teratomectomy.
2. Watson, 1939	19	2 yr.	0	+	5	0	15	+	+	No remission after removal nonspecific ovarian cyst. Remission after splenectomy. Auto-agglutinins found.
3. Singer, Dameshek, 1941	47	5 mo.	+	+	5.1	+	46	+	×	Short remission after splenectomy. Complete remission after ovariectomy.
4. Jones, Tillman, 1945	35	1 mo.	×	+	5	+	10	+	+	Slow recovery following removal pseudomucinous cystadenocarcinoma. Pt. had dermatomyositis.
5. Lindeboom, 1950	40	yrs.	+	+	4.3	×	16	+	+	No remission after splenectomy. Emergency surgery for intestinal obstruction due to teratoma. Died at surgery.
6. Allibone and Collins, 1951	5	3 mo.	×	+	7	+	39	+	0	Completely normal hemogram 3 days post-teratomectomy. Sustained.
7. de Gruchy, 1954	61	9 mo.	0	0	5.2	+	20	+	×	Died of transfusion reaction. Normal spleen and ovarian dermoid at post mortem.
8. Present case, 1955	26	1 yr.	+	+	3.6	+	58	+	+	Rapid sustained remission following teratomectomy.
9. Suarez, Etcheverry, 1936	73	13 yr.	+	+	RBC 1–2 mil.	+	Elevated	+	×	Pt. died 1 day after removal of spleen and teratoma attached to splenic pedicle. Multiple transfusions during 13 years of illness.
10. Sande, 1953	30	×	+	+	5.8	+	60	+	+	Partial remission with ACTH. Sustained remission after removal mesenteric cyst. Coombs became neg. 10 mo. post-op. Cyst fluid yielded high concentration antibodies.

The last two cases are included, although no ovarian tumor was present, because of the similarity to the other cases. It should be noted that Watson's case was not a teratoma, and that the spherocytosis seen in all other cases was absent. All patients were female. Our patient is the only Negro in the group.

+ = present; 0 = absent; × = no information.

History revealed that the patient had lived a normal life, marred only by the usual diseases of childhood and adolescence. There was no history of hemolytic disease, leg ulcer or episodes suggesting sickle cell crisis. Members of her family had no known familial diseases, including those of hemolytic nature. Repeated determinations of hemoglobin during nurses' training had been "above 90%." During her first pregnancy, in 1952, she was examined and her hemoglobin found to be 14 gm.%.

The onset of her illness occurred in January, 1954, one or two weeks following the termination of her second pregnancy in a spontaneous abortion. At this time the patient experienced chronic fatigue, generalized myalgia, headache, palpitation and exertional dyspnea. Her physician examined her and said that she had a tumor of either the uterus or the ovary, and that her complaints were the aftermath of the recent abortion. During the ensuing months the patient noted increasing incapacity due to the progression of the above symptoms. In July, 1954, she noted definite scleral icterus and dark urine. She sought medical aid and was hospitalized. Following hospital study the patient was told that she had sickle cell anemia. She was given multiple transfusions without improvement in her condition. She was therefore placed on 40 u. intermuscular ACTH, self-administered daily. Despite this therapy the patient required one to three whole blood transfusions weekly to maintain strength for minimal activity. The steroids caused a 35 pound weight gain. Weekly transfusions were continued from July through December, 1954, at which time the patient visited Washington, D. C., and shortly presented herself at Walter Reed seeking transfusion.

Physical examination revealed steroidal facies and obesity in a young Negro female with moderate icterus and pallor. There was a grade I blowing basal systolic murmur. The liver edge was palpable at the costal margin, and the spleen was easily palpable 3 cm. below the costal margin. An irregular 10 by 8 cm. mass was palpable in the right pelvis on abdominal and vaginal examination. Slit lamp examination revealed red cell agglutination within the vessels of the scleral conjunctivae.

Initial laboratory studies showed a leukocytosis of 11,900, with a normal differential, and a platelet count of 227,000; red cells, 2.6 million; hematocrit, 26; hemoglobin, 8.4 gm.; reticulocytes, 26%. Blood indices: MCV, 100; MCH, 35.6; MCHC, 35.6. Peripheral blood smear showed many spherocytes, polychromatophilia, anisocytosis, poikilocytosis, and 20 nucleated red blood cells per 100 white blood cells. Osmotic fragility was increased. A sickle cell preparation showed 80% sickling. Total serum bilirubin was 2.2 mg./100 ml., with 1 mg. of direct-reacting bilirubin. Smear of marrow aspirate showed a marked erythroid hyperplasia. It was obvious that the patient had a severe hemolytic anemia. The direct and indirect Coombs' tests were positive, and warm agglutinins were demonstrated. This indicated a diagnosis of autoimmune hemolytic anemia.

Steroids were stopped and transfusions were withheld to learn whether the patient's hemoglobin would stabilize at a reasonable level. Ten days following her admission the hemoglobin had dropped to 3.6 gm. and the reticulocyte count had risen to 58%. Peripheral blood smear contained 103 nucleated red blood cells per 100 white blood cells. The uncorrected leukocyte count was 40,000. Paper electrophoresis of the patient's hemoglobin at this time showed her to be heterozygous SA, thus eliminating the diagnosis of sickle cell anemia. To establish the rate of hemolysis the patient was transfused with normal, compatible Cr^{51} tagged red cells. Within five hours 60% of the transfused cells had been destroyed and only 10% of the cells remained in her circulation at 42 hours (figure 1). Tagged red cells from the patient were transfused into a normal recipient. Within seven days 28% of the cells had been eliminated, and at 21 days only 5% remained (figure 1). Evidently the cells from the patient had been irreversibly damaged by the auto-immune process,

so that they survived poorly even in a normal circulation. The patient was now transfused with washed, packed red cells, so that a hemoglobin level of 14.7 gm. was attained, and 12 days after admission a teratoma of the left ovary measuring 10 by 15 cm. was removed (figure 2). The histologic picture was that of adult cystic teratoma. No lymphocytic tissue or tissue resembling bone marrow was found. The postoperative course was singularly smooth. The patient required no further therapy. The hemoglobin declined to 12.2 gm. three days postoperatively, but at seven weeks reached 14.7 gm., with a reticulocyte count of 1.2% and no spherocytosis. The spleen had shrunk beneath the costal margin. The direct Coombs' test remained positive.

It may have been somewhat fortuitous that the patient experienced an acute pyelonephritis four weeks postoperatively, with temperature elevation to 105° F.

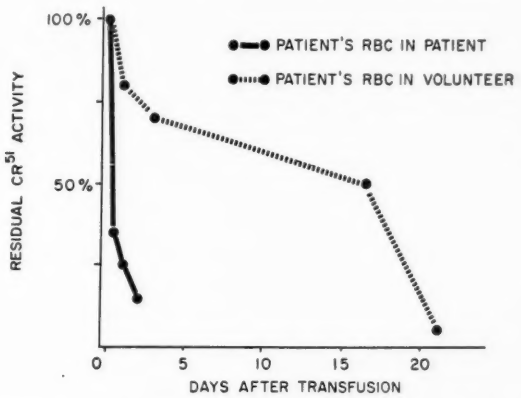


FIG. 1. Survival of Cr^{51}-tagged red blood cells in autoimmune hemolytic disease associated with an ovarian teratoma.

Such challenges frequently cause relapses in auto-immune hemolytic anemia, but our patient showed no evidence of relapse. As of the time of writing she continues to enjoy good health.

DISCUSSION

This is the tenth reported case in which auto-immune hemolytic anemia has been associated with an ovarian tumor or a dermoid elsewhere in the body.[1, 9] In six cases a cure followed removal of the teratoma. Three died. In one case the removal of an ovarian tumor did not result in improvement, but a subsequent splenectomy was followed by remission of the hemolytic disease.[2] It may be significant that the ovarian cyst in this case was not a dermoid. It is also of some interest that this was the only case in which spherocytosis was noted to be absent. In other forms of auto-immune hemolytic anemia the presence of spherocytosis is inconstant, occurring in perhaps 50% of the cases.

The presence of intense spherocytosis in the present case was a cause of some diagnostic concern as to whether this might not be a case of hereditary spherocytosis. The positive Coombs' test is not an absolute criterion.[13] Patients with hereditary spherocytosis have been known to develop auto-immune crises with

a transitory positive Coombs' test. This woman also had sickle cell trait, but that too is not incompatible with the diagnosis of hereditary spherocytosis, since coincidence of the two diseases has been reported. A family study might have helped, but the family was not available.

Precise diagnosis was important, since splenectomy can cure hereditary spherocytosis, and teratomectomy can cure this type of symptomatic hemolytic anemia. The decision for teratomectomy in this case was based on "preponderance of evidence." The tumor was removed and the spleen was not. Thereupon the spherocytosis and hemolysis disappeared.

The intense erythroblastosis was another source of interest and concern, since it is supposed to indicate a poor prognosis. It is often considered to be a sign of extramedullary hemopoiesis. It could be speculated that the splenomegaly in this case was due to myeloid metaplasia.

Steroid therapy with or without splenectomy for auto-immune hemolytic disease offers insecure remission in only 50% of trials. The hemolytic process associated with teratomas is usually unresponsive to such therapy but is cured readily by teratomectomy. This is brought into clear focus by the tabulated review, and demonstrates the validity of clinical conclusions drawn from experiences too small to undergo statistical analysis.

Summary

1. A case is reported of auto-immune hemolytic anemia associated with an ovarian teratoma in a Negro woman with sickle cell trait and severe spherocytosis. The anemia was cured by removal of the tumor. The spherocytosis disappeared and the splenomegaly subsided.

2. The literature has been reviewed, and 10 cases are tabulated.

3. The differential diagnosis is commented upon.

Summario in Interlingua

Es reportate un caso de anemia hemolytic auto-immun que esseva arrestate per le ablation de un teratoma ovarian. Es presentate un revista del litteratura pertinente.

Anemia hemolytic auto-immun es characterisate per le formation de anticorpores per le patiente contra su proprie erythrocytos. Symptomatic anemia hemolytic auto-immun es le forma del morbo que es causate per conditiones diagnosticabile, i.e. per exemplo pneumonia virusal, mononucleosis infectiose, syphilis, e sarcoidosis. Le morbo primari es usualmente auto-limitante o responde al tractamento, e assi le processo hemolytic es arrestate. Symptomatic anemia hemolytic auto-immun pote etiam occurrer con neoplasias, que es generalmente maligne e mortal. Le association de anemia hemolytic auto-immun con teratomas e cystes mesenteric es importante proque le ablation del tumor benigne arresta le processo hemolytic que es frequentemente invalidante e mesmo mortal.

Le patiente del presente reporto es un maritate feminina negre de 26 annos de etate qui disveloppava symptomas del typo characteristic de anemia duo septimanas post un aborto spontanee in januario 1954. A ille tempore un massa pelvic esseva notate. Le symptomas progredeva usque julio 1954 quando ictero esseva notate pro le qual le patiente esseva hospitalisate. Illa esseva tractate con transfusiones septimanal e 40 unitates de ACTH per die usque januario 1955 sed sin melioration.

Al tempore de iste admission al hospital, le examine physic revelava ictero, anemia, splenomegalia, e un massa pelvic. Studios laboratorial demonstrava signos de un

sever processo hemolytic, con positivitate in le tests de Coombs e pro auto-agglutininas calide. Electrophorese a papiro constatava le presentia del tracto de cellulas falciforme.

Spherocytosis de grados intense esseva presente e disquietante ab le puncto de vista diagnostic, proque spherocytosis hereditari in stato de crise pote duplicar le constatationes notate, e nulle consanguineos esseva disponibile pro le execution del essayos appropriate. Tamen, le datos pareva preponderar in favor de un operation pelvic plus tosto que de splenectomia, e un adulte teratoma ovarian cystic de dimensiones de 10 per 15 cm esseva excidite. Le processo hemolytic, le spherocytosis, e le splenomegalia subsideva e non ha retornate in le curso de 12 menses de observation post-operatori.

Un tabulation de 10 reportate casos de anemia hemolytic auto-immun in association con teratoma ovarian es presentate in tabula 1. Therapia steroide con o sin splenectomia produce insecur remissiones in solmente 50 pro cento del patientes con anemia hemolytic auto-immun e non ha succedite in casos de iste morbo que esseva associate con teratomas ovarian. Le ablation del tumor es dramaticamente curative.

BIBLIOGRAPHY

1. West-Watson, W. N., and Young, C. J.: Failed splenectomy in acholuric jaundice and the relation of toxaemia to the haemolytic crisis, Brit. M. J. **1**: 1305, 1938.
2. Watson, C. J.: Hemolytic jaundice and macrocytic hemolytic anemia: certain observations in a series of 35 cases, Ann. Int. Med. **12**: 1782, 1939.
3. Singer, K., and Dameshek, W.: Symptomatic hemolytic anemia, Ann. Int. Med. **15**: 544, 1941.
4. Jones, E., and Tillman, C.: A case of hemolytic anemia relieved by removal of an ovarian tumor, J. A. M. A. **128**: 1225, 1945.
5. Lindeboom, G. A.: Rare forms of hemolytic anemia, Acta haemat. **4**: 343, 1950.
6. Allibone, E. C., and Collins, D. H.: Symptomatic haemolytic anaemia associated with ovarian teratoma in a child, J. Clin. Path. **4**: 412, 1951.
7. de Gruchy, C. C.: The diagnosis and management of acquired haemolytic anaemia, Australasian Ann. Med. **3**: 106, 1954.
8. Suarez, C. V., and Etcheverry, M. A.: A ciste dermoidea del hilio esplenico esplenomegalia icterica hemolitica y anemia grava, Arch. argent. de enferm. d. ap. digest. y de la nutrición **12**: 168, 1936–37.
9. Sande, Af E.: Immunhaemolytiskanaemi; Overvejelser angaende det irregulaere antisotofs oprindelse foranlediget as et tilfaelde af et tilfaelde of immunhaemolytisk anaemi med samtidig forekomst as en mesenterialcyste met et stort indhold af antistof., Nord. med. **50**: 1565, 1953.
10. Dameshek, W.: Hemolytic anemia: direct and indirect indications, pathogenetic mechanisms and classifications, Am. J. Med. **18**: 315, 1955.
11. Dacie, J. V.: The haemolytic anaemias, congenital and acquired, 1954, Grune and Stratton, New York.
12. Rosenthal, M. C., Pisciotta, A. V., Komninos, Z. D., Goldenberg, H., and Dameshek, W.: The auto-immune hemolytic anemia of malignant lymphocytic disease, Blood **10**: 197, 1955.
13. Crosby, W. H.: The hemolytic states, Bull. New York Acad. Med. **30**: 27, 1954.
14. Crosby, W. H.: The metabolism of hemoglobin and bile pigment in hemolytic disease, Am. J. Med. **18**: 112, 1955.

POLYCYTHEMIA ASSOCIATED WITH A BENIGN KIDNEY LESION: REPORT OF A CASE OF ERYTHROCYTOSIS WITH HYDRONEPHROSIS, WITH REMISSION OF POLYCYTHEMIA FOLLOWING NEPHRECTOMY *

By William M. Cooper, M.D., and William B. Tuttle, M.D.,
Pittsburgh, Pennsylvania

Introduction

Erythrocytosis has been reported in association with a wide variety of pathologic states: exposure to low atmospheric oxygen pressure, heart disease and in particular the cyanotic group of congenital heart disease, arteriovenous fistulas, endocrine disorders such as Cushing's syndrome, intracranial tumors, the pulmonary diseases characterized by decreased respiratory exchange, obesity, fibromyomas of the uterus, and intoxication by, or exposure to, analine, phosphorus, cobalt and certain other chemicals.[1, 2, 3, 4, 5, 6]

Grant and Root reviewed the experimental data concerning the fundamental stimulus for erythropoiesis in their comprehensive article in 1952.[7]

The unique relationship of hypernephroma and polycythemia has been reported in nine instances,[8, 9, 10, 11] and benign adenoma of the kidney and polycythemia in one instance.[12]

Forssell [8] first suggested that hypernephroma be classed among the tumors causing polycythemia, and reported four such cases. The first patient was observed for three years, during which time there was a sequence of hematuria, polycythemia, and discovery and removal of a hypernephroma, followed by remission of the polycythemia. Subsequently, polycythemia returned, and 14 months after discovery of the initial neoplasm a hypernephroma was discovered in the remaining kidney at autopsy. Of Forssell's three additional cases, one was without histologic proof of tumor. One case had widespread metastases to the lungs and left adrenal gland. The final case may not have represented true polycythemia because the highest of four red blood cell counts was 6,184,000 per cubic millimeter, which is slightly below the generally accepted upper limit of normal. Autopsy revealed a large, invasive hypernephroma, but no mention was made of the extent of metastases or other pathologic findings. This case is notable, however, in that renal carcinoma is frequently associated with anemia.

Videbach [9] reviewed the autopsies of 35 patients with polycythemia and found hypernephroma in two. One case had widespread pulmonary metastases. The second case also had severe cystopyelonephritis, and the only metastatic lesion observed was a solitary nodule in the liver. Videbach also reported a case of polycythemia with hypernephroma, which was treated by venesection and radioactive phosphorus, and subsequently by nephrectomy. Postoperative observation was limited to six months, during which time the patient had no return of polycythemia.

* Received for publication March 1, 1957.

From the Medical Service, Veterans Administration Hospital, Pittsburgh, Pennsylvania, and the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

Requests for reprints should be addressed to W. M. Cooper, M.D., Pittsburgh Diagnostic Clinic, 3501 Fifth Avenue, Pittsburgh 13, Pennsylvania.

Fairley [10] reported two cases of what he called Gaisböck's disease associated with carcinoma of the kidney. The first case was observed for five years. During that time polycythemia was noted for one year prior to hematuria. After 29 months of hematuria a nephrectomy was performed for a lesion identified as renal adenocarcinoma with clear cells. Postoperatively neither polycythemia nor clinical evidence of metastases was observed in the two years preceding the patient's death from cerebral hemorrhage. The second patient had polycythemia and bronchogenic carcinoma with widespread metastases. Renal function was impaired, and autopsy showed that multiple metastases had largely destroyed both kidneys.

Lawrence [11] mentioned three deaths attributable to neoplastic disease in a study of 172 patients with polycythemia vera. One of these was said to have been due to carcinoma of the kidney; however, no further information concerning the case was presented.

DeMarsh and Warmington [12] reported a case of a young girl in whom the presence of a right renal tumor and polycythemia had been known for at least five years. Right nephrectomy induced a remission in the polycythemia which persisted throughout a five-year follow-up period. The specimen consisted of a 7 cm. benign adenoma and normal renal tissue.

The case here described represents an instance of polycythemia occurring in association with hydronephrosis. Such an association has not heretofore been described in the literature.

Case Report

A 55 year old mill supervisor was admitted to the hospital on April 12, 1950. For one year prior to admission he had experienced progressively increasing fatigability, weakness, anorexia, daily headaches and lightheadedness. The past history revealed that at eight years of age the patient had had "Bright's disease," lasting for two years. There had been no other significant illness prior to the onset of the presenting symptoms.

Physical examination revealed a florid, slightly obese middle aged white male in no distress. The blood pressure was 150/100 mm. of Hg; temperature, 98.6° F.; pulse, 88; respirations, 20.

Complete physical examination revealed no significant abnormalities except a large left upper quadrant abdominal mass which was rounded and slightly tender. The mass did not move with respirations, and transmitted a faint lateral pulsation.

Urinalyses revealed persistent proteinuria and microscopic pyuria and hematuria. The serologic test for syphilis was negative. Serum bilirubin was 0.93 mg.; nonprotein nitrogen, 41 mg.; fasting blood sugar, 75 mg.; serum cholesterol, 295 mg. per 100 c.c. The prothrombin time, bleeding time and coagulation time were normal. A bromsulfalein test showed 10% retention in 45 minutes. There was no abnormal retention of Congo red. Excretion of phenolsulfonphthalein was 28% in 30 minutes and 49% in four hours. A Fishberg concentration test revealed specific gravities of 1.012 and 1.014. The basal metabolic rate was reported as 0. Bone marrow obtained by the aspiration technic was normal.

Serial hemograms are listed below and include values reported during hospitalization and the ensuing six years (table 1).

A survey film of the abdomen showed enlarged kidney outlines bilaterally and multiple calcific densities in the left mid and lower abdomen. Intravenous and retrograde pyelograms were made (figure 1). The left kidney was functionless, and retrograde filling of the left ureter ended abruptly in a region of calcification.

The right ureter and kidney were well visualized in the intravenous pyelogram, and the calyceal system showed changes slightly suggestive of polycystic disease.

X-ray of the gall-bladder and barium enema revealed no abnormal findings. A gastrointestinal series revealed displacement of the stomach to the right by an extrinsic mass in the left upper quadrant of the abdomen.

Roentgenograms of the chest, including laminagraphic studies, revealed a saccular aneurysm of the distal portion of the aortic arch.

By the Evans blue method, plasma volume was 2,840 c.c. (predicted plasma volume, 3,020 c.c. $\pm$ 240 c.c.). The total blood volume was 7,750 c.c. (predicted blood volume, 5,800 c.c $\pm$ 600 c.c.)

An electrocardiogram showed minor T wave abnormalities.

The patient remained afebrile during hospitalization. Following the initial hematologic studies, 2,200 c.c. of blood were removed by venesections, and prompt improvement in the patient's symptoms was noted.

TABLE 1

Serial Blood Cell Counts and Hematocrit Determinations on the Patient during Hospitalization in 1950 and during the Ensuing Six Years

DATE	RED BLOOD CELL COUNT PER CU. MM.	HEMOGLOBIN	HEMATOCRIT	WHITE BLOOD CELL COUNT PER CU. MM.	PLATELETS
4-13-50	6,380,000	17.5		11,300	
4-26-50	9,850,000	19.0	66	8,000	308,000
5-9-50	8,290,000	18.5		6,400	360,000
5-15-50	7,200,000	19.0	68	7,000	
FOUR VENESECTIONS TOTALING 2200 CC FROM 5-20-50 TO 5-31-50					
6-5-50	5,240,000	16.0	50	7,500	
6-29-50	5,490,000	16.0		9,000	302,000
NEPHRECTOMY 7-3-50					
7-19-50	4,020,000	15.0	47	9,600	
9-21-50	4,290,000	13.5	41	9,200	230,000
7-2-51	4,840,000	13.5	44	11,300	246,000
3-9-55	4,740,000	14.5	46	10,100	316,000
4-25-56	4,380,000	13.0	44	8,500	260,000

On July 3, 1950, left nephrectomy was performed. Two hydronephrotic sacs, containing approximately 2,000 and 1,000 c.c. of cloudy material, respectively, were encountered and removed with the residual left renal tissue. The specimen (figure 2) measured 21 by 10 by 5.5 cm. and was a multiloculated cystic structure. The parenchyma was completely replaced with thin-walled cysts communicating with the pelvis. The cysts had a grayish pink lining and were filled with cloudy yellow fluid. One cyst contained eight smooth brown calculi, the largest of which was 0.8 mm. in diameter. At the ureteropelvic junction there was an irregular black stone measuring 3 cm. in diameter. This large calculus had nodular prolongations which filled the orifices of three calyces as well as the ureter. Microscopic examination showed almost complete replacement of renal parenchyma by dense scar tissue which formed the cyst walls. The cysts were partially lined by transitional epithelium. One section showed diffuse interstitial scarring, periglomerular fibrosis, and endothelial proliferation of the small vessels. Chemical examination of the calculi showed prin-

cipally calcium urates. The pathologic diagnosis was severe left hydronephrosis secondary to ureteropelvic obstruction by renal calculus.

Following operation the patient's hospital course was uneventful, and he was discharged on the eighteenth postoperative day. Eleven weeks postoperatively the

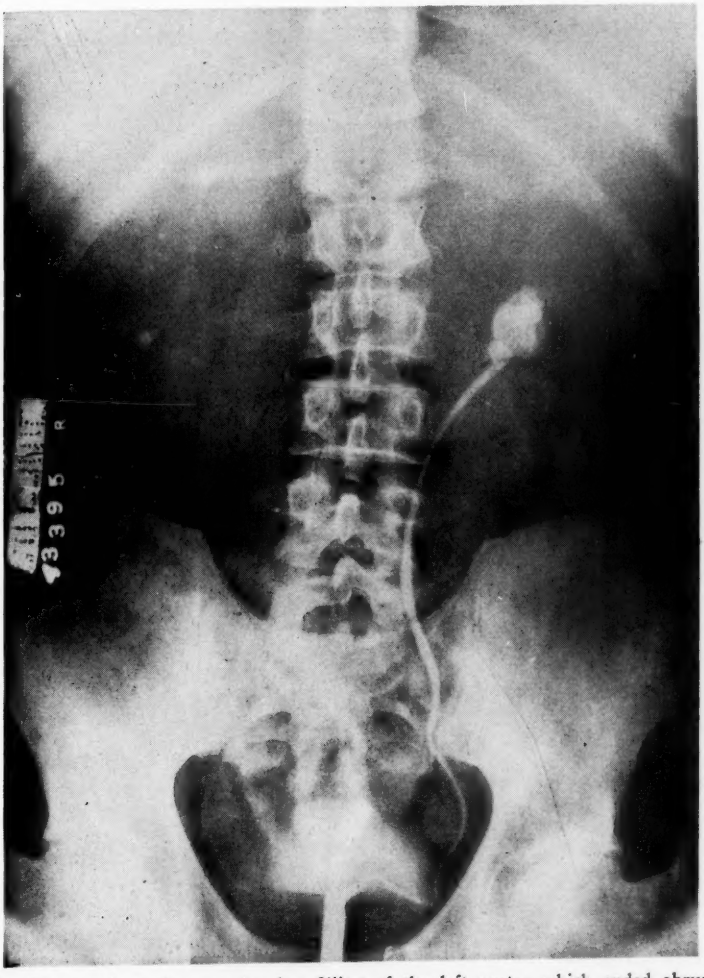


FIG. 1. Retrograde pyelogram showing filling of the left ureter which ended abruptly in a region of irregular calcification.

patient was asymptomatic, and anxious to return to work. His hemogram was normal, as shown in the table (September 21, 1950). Only July 2, 1951, no changes were observed in the patient's clinical findings.

The patient had no symptoms on March 9, 1955, five years after initial study. Examination revealed the blood pressure to be 128/84 mm. of Hg. His complexion

was no longer florid, and there were no abnormal abdominal masses. His weight had increased from 134 to 164 pounds since 1950. As noted in table 1, the hemogram had remained normal. The urine showed a specific gravity of 1.022, and there was no proteinuria or abnormal microscopic findings. Nonprotein nitrogen was 39 mg., uric acid, 5.5 mg.; total protein, 6.6 gm., with albumin 4.2 gm., and globulin, 2.4 gm.

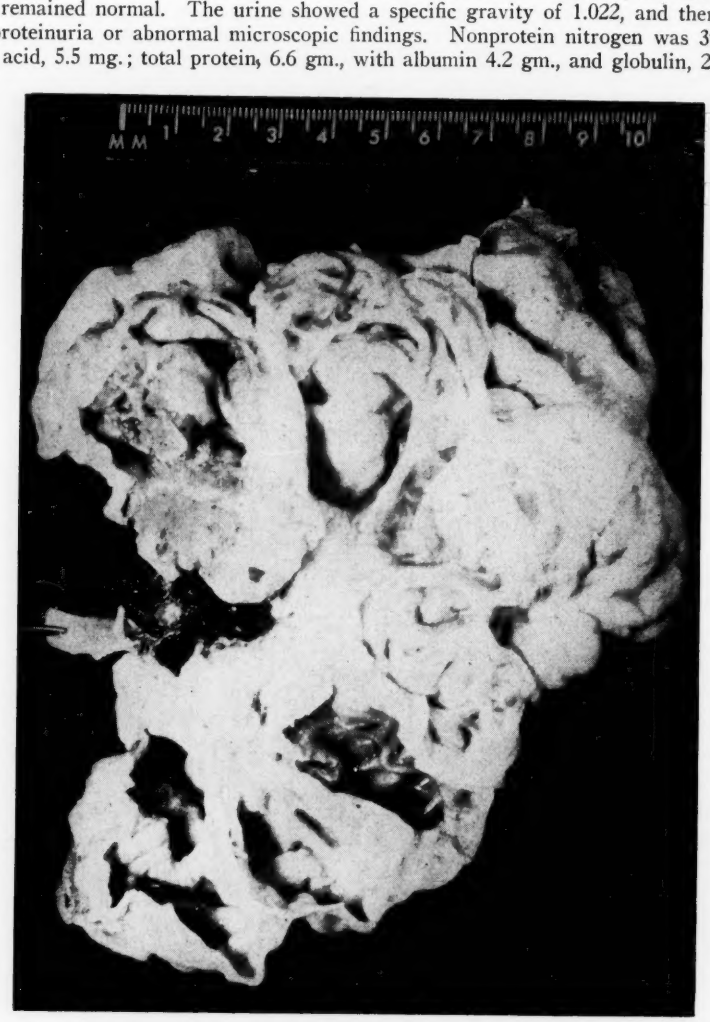


FIG. 2. Surgical specimen of left kidney which revealed a large calculus obstructing the ureteropelvic junction. The renal parenchyma was replaced by thin-walled cysts and fibrous tissue.

per 100 c.c. X-ray of the chest showed no change when compared with the films taken in 1950.

The patient's final admission was on April 25, 1956. For one year he had observed gradual progression of cough, hoarseness, dyspnea, weakness, and substernal pain which radiated to the back and left arm. Physical examination revealed a

dyspneic 62 year old male who was hoarse and had paroxysms of coughing described as "brassy." There was an area of increased tactile fremitus and bronchial breathing localized to the first left intercostal space in the parasternal line. The peripheral pulses were all palpable. Urinalysis revealed a negative test for protein and a specific gravity of 1.016. The nonprotein nitrogen initially was 31 mg., rising to 56 mg. on May 10, 1956. A complete blood count was normal, as noted in table 1. X-rays of the chest confirmed the clinical impression of a marked increase in the size of the aneurysmal dilatation of the aorta since the examination one year previously. The patient had a progressive increase in his symptoms and died on May 24, 1956.

At autopsy a large pulmonary infarction was found. There was atelectasis of the left upper lobe secondary to a saccular aneurysm of the aortic arch. There was marked arteriosclerosis of the aorta and coronary arteries. Compensatory hypertrophy of the right kidney was noted. Sections of the spleen revealed marked congestion with erythrocytes and a few small groups of myelocytes and normoblasts. There was slight generalized hypoplasia of the bone marrow.

Discussion

This is the first instance of polycythemia associated with hydronephrosis to be reported in the literature. The diagnosis of erythrocytosis was established by repeated blood cell counts and blood volume determination. Following venesections and the removal of a hydronephrotic left kidney, the blood counts returned to normal and remained normal during a six-year period of observation, suggesting a causal relationship between the diseased kidney and the polycythemia.

The nine reports of polycythemia in association with hypernephroma include three instances in which remission of polycythemia followed removal of the malignant lesion. A single case has been reported in which a five-year remission of polycythemia followed the removal of a benign adenoma of the kidney. The sequence of events in our case was similar, and suggests the possibility of a common erythrogenic factor in all these cases not related to the presence of neoplastic tissue.

The mechanism of erythropoietic overproduction in relation to renal disease is not well understood. In cases of malignant renal tumors with metastases, anoxia produced by lung or bone marrow invasion may play a predominant role in stimulation of erythroid tissue.

Hematuria was present in every reported case of hypernephroma with polycythemia. Hematuria was also present in our case of hydronephrosis. It is doubtful that this chronic blood loss provided a stimulus potent enough to produce polycythemia.

Obesity and large intra-abdominal masses such as uterine fibromyomas may possibly restrict respirations by virtue of an increased volume of the abdominal contents resulting in hypoxemia.

The pituitary, adrenal and thyroid glands have been implicated in the production of erythrocytosis; however, their exact role has not been defined. Neither in the cases with renal tumors nor in our patient with hydronephrosis was endocrine dysfunction apparent on a clinical basis.

Experimental studies of the stimulus for erythropoiesis suggest certain mechanisms which could theoretically have played a part in our case.[7]

Various erythrogenic humoral factors have been suggested. It is possible

that products of bacterial or neoplastic degeneration may stimulate the production of or mimic the effect of an erythrogenic factor. Experimentally, products of blood destruction have been shown to have an erythrogenic effect. There was no evidence of a significant degree of hemolysis in our case.

Kidney tissue may normally stimulate erythropoiesis. Diets rich in kidney tissue have been reported to have an antianemic effect. Renal tissue is known to have an avidity for vitamin B_{12}. There may be a significant relationship between these observations and the association of polycythemia with renal disease.

The authors suggest that the mechanism of this association be investigated further by endocrine analyses and animal testing of renal tissues obtained from cases found to have polycythemia and either benign or malignant renal disease.

Summary

A 55 year old man was found to have polycythemia and left hydronephrosis. Removal of the hydronephrotic kidney produced a remission of the polycythemia which persisted for the remaining six years of his life. Death was due to unrelated disease.

Reference is made to nine reported cases of renal carcinoma associated with polycythemia, three of whom had remission of polycythemia following nephrectomy, and one case of a benign renal tumor in which nephrectomy produced a five-year remission of polycythemia. The possibility that a common erythrogenic factor exists is suggested by the similarity between those cases and this instance of hydronephrosis. The cause of polycythemia associated with renal disease remains obscure.

Summario in Interlingua

Le 12 de april 1950, un masculo blanc de 55 annos de etate esseva admittite al hospital con le gravamines de progressive fatigabilitate, debilitate, anorexia, mal de capite, e episodios de confusion—omnes de un duration de un anno. Le examine physic monstrava un homine rubicunde, levemente obese, con un pression sanguinee de 150/100 mm de Hg. Esseva notate un grande massa immobile in le quadrante sinistro-superior del abdomine. Le analyse del urina revelava persistente proteinuria e microscopic pyuria e hematuria. Un test del excretion a phenolsulfonphthaleina e un test de concentration secundo Fishberg esseva anormal. Un specimen de medulla ossee obtenite per aspiration esseva normal. Repetite numerationes sanguinee monstrava un persistente elevation erythrocytic, con valores inter 6.380.000 e 9.850.000 per mm^3. Etiam le valores de hemoglobina e del hematocrite esseva elevate. Le numerationes leucocytic e plachettal esseva intra limites normal. Le volumine del plasma esseva 2.840 cm^3 (con un valor predicite de 3.020 $cm^3 \pm 240$). Le volumine total de sanguine esseva 7.750 cm^3 (con un valor predicite de 5.800 $cm^3 \pm 600$). Pyelogrammas intravenose e retrograde revelava un non-functionante ren sinistre que contineva multiple calcificationes. Roentgeno-examines del thorace revelava un aneurysmo saccular del portion distal del arco aortic.

Post venesectiones (con un volumine total de 2.200 cm^3), le numeration sanguinee deveniva normal. Un prompte melioration in le symptomas del patiente esseva observate. Nephrectomia sinistre esseva effectuate le 3 de julio 1950. Le diagnose pathologic esseva sever hydronephrosis sinistre secundari a obstruction ureteropelvic per calculos renal. In le curso del sequente sex annos, le patiente habeva nulle retorno de symptomas e su numerationes hematologic remaneva normal. Le 25 de april 1956 ille esseva re-admittite al hospital a causa de tusse, raucitate, dyspnea, e substernal dolores thoracic. Roentgeno-examines revelava un augmento

in le dimensiones del aneurysmo aortic. Le symptomas progredeva gradualmente, e le patiente moriva le 24 de maio 1956. Le necropsia revelava un grande infarcimento pulmonar. Il habeva atelectasis del lobo sinistro-superior secundari al saccular aneurysmo aortic.

Isto es le prime caso de polycythemia associate con hydronephrosis unquam reportate in le litteratura. Le remission complete del polycythemia post le ablation del ren hydronephrotic suggere le existentia de un relation causal inter le morbiditate del ren e le polycythemia.

Le existentia de un simile relation a polycythemia secundari ha essite reportate pro un grande varietate de morbos. Nove casos de hypernephroma e un caso de adenoma benigne del ren ha essite reportate in association con polycythemia. In tres casos de maligne tumores renal e in un caso (le sol reportate) de benigne tumor renal, nephrectomia induceva prolongate remissiones del polycythemia. Le constatation de un simile curso del evenimentos in le caso del presente reporto suggere le possibilitate del existentia de un commun factor erythrogene.

Un revista del cognoscite e del theoricamente possibile factores contribuente al stimulation erythropoietic non produce un adequate explication del disveloppamento de polycythemia in le presente caso. Le autor suggere que le analyse endocrin e tests con animales applicate al histos renal de simile casos futur va forsan producer un explication del phenomeno in question.

BIBLIOGRAPHY

1. Wintrobe, M.: Clinical hematology, 3d Ed., Chapter 14, 1951, Lea & Febiger, Philadelphia.
2. Goldman, A.: Cavernous hemangioma of the lung: secondary polycythemia, Dis. of Chest **9**: 479, 1943.
3. Perlmutter, I.: Polycythemia complicated by brain tumor, Neurology **4**: 398, 1954.
4. Holmes, C.: Polycythemia secondary to brain tumor, South. M. J. **45**: 967, 1952.
5. Weil, M. H.: Polycythemia associated with obesity, J. A. M. A. **159**: 1592, 1955.
6. Engel, H. W., and Singer, K.: Polycythemia with fibroids, J. A. M. A. **159**: 190, 1955.
7. Grant, W. C., and Root, W. S.: Fundamental stimulus for erythropoiesis, Physiol. Rev. **32**: 449, 1952.
8. Forssell, J.: Polycythemia and hypernephroma, Acta med. Scandinav. **150**: 155, 1954.
9. Videbach, A.: Polycythemia vera co-existing with malignant tumors, Acta med. Scandinav. **138**: 239, 1950.
10. Fairley, K. D.: Two cases of Gaisböck's disease associated with carcinoma of the kidney, Roy. Melbourne Hosp. Clin. Rep. **16**: 47, 1945.
11. Lawrence, J. H.: The control of polycythemia by bone marrow inhibition, J. A. M. A. **141**: 13, 1949.
12. DeMarsh, Q. B., and Warmington, W. J.: Polycythemia associated with a renal tumor, Northwest Med. **54**: 976, 1955.

HEMOCHROMATOSIS AND THE HEART*

By Arnold W. Schreiber, M.D., D.A.B.I.M., *Westbury, New York*

In Sheldon's [1] classic monograph on hemochromatosis, myocardial failure is mentioned as an uncommon cause of death. Several clinical reports of hemochromatosis with cardiac abnormalities have appeared in the literature.[2-9] The

* Received for publication April 21, 1956.
Requests for reprints should be addressed to Arnold W. Schreiber, M.D., 1090 Roxbury Drive, Westbury, N. Y.

following case is presented to emphasize again the occurrence of these entities. In this patient, cardiac catheterization was performed.

Case Report

This was the first admission of a 45 year old single white male, who entered the hospital on June 24, 1952, because of generalized edema.

For the last 15 years the patient had averaged approximately 10 12-ounce bottles of beer per day. Three weeks prior to admission, following an alcoholic bout, he had noted swelling, ascites, and thigh and pedal edema. At about this time jaundice was detected, which persisted for one week. There was no pruritus, clay colored stools or change in the color of urine. During the first few days of the illness there was diarrhea, with brown, watery stools and no blood. This subsided and was followed by moderate constipation. Nineteen days prior to admission there was an episode of epistaxis and slight hemoptysis. Following the onset of the illness three weeks before admission increasing dyspnea on slight exertion, malaise, fatigue and a 20 pound weight gain were noted. In the last three months there had been a 40 pound weight gain. There had been no nausea, vomiting or anorexia. The patient stated that he does not eat when on drinking sprees.

Past History: Not relevant except for alcoholism.

Physical Examination: The patient was a well developed, well nourished white male with slight pallor who appeared older than his stated age. Weight was 201 pounds. Temperature, pulse and respirations were normal. Blood pressure was 134/96 mm. of Hg in the right arm and 110/76 mm. of Hg in the left arm. There was marked venous congestion of neck veins bilaterally in all positions. The sclerae were slightly icteric. There were dullness and absent breath sounds at the right base. The heart had a normal sinus rhythm, the sounds were of good quality, and A_2 was greater than P_2. A systolic murmur and a soft diastolic murmur were heard at the aortic area and at the left sternal border. The abdomen was protuberant, with shifting dullness. The liver edge was palpated three fingerbreadths below the costal margin. The genitalia were edematous. There were 2 plus pitting edema of the feet and ankles, and 1 plus edema of the thighs. There were one spider nevus on the left shoulder and a few dilated superficial veins over the abdomen. Palmar erythema was present bilaterally.

Laboratory Data: On admission, the urine was negative for sugar and albumin, and negative microscopically. Specific gravity was 1.008; bile was absent, and urobilinogen was 0.1 Ehrlich unit. The white blood cell count was 5,250, with 62% neutrophils, 35% lymphocytes and 3% monocytes. Hemoglobin was 13.5 gm.%. Serologic test for syphilis was negative. Erythrocyte sedimentation rate (Wintrobe), 3 mm./hr.; hematocrit, 43; nonprotein nitrogen, 34 mg.%; fasting blood sugar, 90 mg.%; prothrombin time, 44%; icteric index, 12 units; serum bilirubin: total 2.2, 0.25 direct; bromsulphalein retention, 34.5%; cephalin flocculation, 2 plus; alkaline phosphatase, 3.1 Bodansky units; total protein, 7.7 gm.%; AG ratio, 1:1. Repeated stool examinations were negative for ova, parasites and occult blood. Sputa examinations were consistently negative. Repeated liver function studies in one month and in six weeks were essentially unchanged.

Chest film on admission revealed generalized cardiac enlargement, with no evidence of any specific chamber enlargement. There was a small pleural effusion at the right base. Repeated roentgenograms on July 7 and July 17 revealed no change except for absorption of pleural fluid. The patient was digitalized on July 12, and a chest film on August 8 revealed cardiac enlargement of all chambers, as previously described, but with diminution of the cardiac size.

An electrocardiogram taken on June 26 showed N.S.R., low voltage, a PR

interval of 0.22, and inverted T waves in Leads I, II, III and AVF, also in V_2 through V_6. Repeated electrocardiographic tracings revealed the persistence of the first degree heart block, low voltage and inverted T waves. On August 2 there was a change in rhythm to an auricular flutter-fibrillation.

Clinical Course: On admission the patient was placed on a low salt, high protein, low fat diet, with vitamin supplements and choline. No digitalis was given at this time. Within five days on this régime there was a decrease in weight of 17 pounds. The temperature, pulse and blood pressure remained stable. Venous pressure on admission was 370 mm. of water, and circulation time (Decholin) was 58 seconds. The patient continued to have dyspnea on exertion, but during the next week began to feel better. Repeat circulation time on July 4 was 32 seconds, the neck veins were still distended and the venous pressure was 430 mm. of water, with a positive hepatojugular reflex. On July 10 the venous pressures were: right arm, 300 mm. water; left arm, 330 mm. water; right leg, 260 mm. water. It was felt at this time that the maximal improvement with bed-rest and low salt diet had been obtained, and the patient was slowly digitalized over the next two days (July 12 to 14). A diuresis of 3,500 c.c. occurred, after which the patient was able to lie flat in bed. The pulse rate remained regular and slowed to 68 per minute. Two days later the circulation time was 31 seconds. The following week the weight had dropped to 163.5 pounds, the venous pressure was 130 mm. water, and the circulation time 24 seconds. During this period of time Mercuhydrin, 2 c.c., had been given on one occasion. On July 23 cardiac catheterization was performed in an attempt to elucidate the cause of the congestive heart failure.

On the day of catheterization the patient was kept in a fasting state. Preoperative medication of Seconal, 0.1 gm., and Demerol, 75 mg., as well as 750 mg. of Pronestyl, was administered. Cardiac catheterization was performed by the Cournand [10] technic. Pressures were recorded by calibrated Sanborn electromanometers.[11] Oxygen consumptions were performed by the Benedict-Roth method; hence, the patient was breathing pure oxygen during the time of the sampling of the blood. Exercise was performed by having the patient flex the knees and the thighs for several minutes. Blood samples were analyzed for oxygen content, capacity and saturation by the method of Van Slyke and Neill,[12] and the arteriovenous oxygen difference was calculated. The results are tabulated in table 1.

During the next week the maintenance dose of digitalis was increased from 0.1 gm. to 0.2 gm. of the leaf per day. Circulation time was now 21 seconds and venous pressure 130 mm. of water. On August 2 the pulse was irregular, and an electrocardiogram revealed auricular fibrillation-flutter. The digitalis dosage was readjusted and normal sinus rhythm returned. For the next month the patient's activities were gradually increased. Because of poor liver function, a liver biopsy was not performed. Treatment now consisted of a low sodium diet, digitalis, multivitamins, and one injection of Mercuzanthin on August 30. At this time nausea began, and a gain in weight of 8 pounds had developed. There was also a return of pedal edema, jugular vein distention, some orthopnea and a diminished urinary output compared to water intake. Blood CO_2 was 18 mEq.%, and chlorides were 90 mEq.%. It was felt that a low sodium syndrome had occurred, and therapy with hypertonic saline was begun. Despite large amounts of saline, the patient's course was progressively downhill. The urinary output decreased to 100 c.c., cyanosis developed, the heart rate was 42 per minute and dyspnea increased. Nonprotein nitrogen was 57.5 mg.%. The patient suddenly gasped and died on September 1, 1952.

Autopsy Report: The patient was a middle aged white male with bilateral 1 plus leg edema. The abdominal cavity contained 3,500 c.c. of clear, straw-colored fluid. Each hemithorax contained 400 c.c. and the pericardium 120 c.c. of similar fluid. The lungs were congested and the lower lobes slightly atelectatic. The heart

was symmetrically enlarged and weighed 500 gm. It was more dilated than hypertrophied, and the myocardium was of the usual color. On the posterolateral wall of the right atrium was an area of white scarring measuring 5 by 4 cm. The right ventricular wall measured 3 mm. in thickness and the left ventricular wall 10 mm. There were numerous small old thrombi attached to the posterior wall of the right atrium and auricle. The heart valves were not remarkable. The coronary ostia were patent. Numerous atheromatous plaques were found in the coronary arteries without any evidence of obstruction or thrombi. The aorta revealed a few scattered atheromatous plaques. The spleen was enlarged and weighed 875 gm. The liver weighed 1,900 gm. and was slightly enlarged. The color was deep brown. It had a grossly nodular appearance and cut with increased resistance. On section, the liver was a deeper brown, and had a firm granular surface and an accentuation of its

TABLE 1

Cardiac Catheterization Data

Age 45
Ht. 173 cm.
Wt. 74 kg.
BSA 1.88
Rm. temp. 23.5° C.

	Rest	Exercise
O_2 consumption (c.c./min.)	228.8	743.7
(c.c./min./M²)	121.7	395.5
Arterial O_2 content (vol. %)	22.93	23.56
Pul. art. O_2 content (vol. %)	17.55	15.42
AV O_2 difference (vol. %)	5.38	8.14
Cardiac output (L./min./M²)	4.25	9.14
Cardiac index (L./min./M²)	2.26	4.86
Arterial O_2 capacity (vol. %)	23.21	23.21
Arterial O_2 saturation (%)	99	101

Pressures (mm. Hg)	Systolic	D1	D2	MP	PP	Ht. Rate
Rt. "PC"—rest				11		68
Rt. PA—rest	28		11	16	17	67
exercise	29		11	18	18	68
Rt. ventricle—rest	29	1.5	7	14	22	68
Rt. auricle—rest				5		68
Brachial artery—rest	115		70	85	45	75

markings. Thin slices of tissue stained a deep blue with potassium ferrocyanide. The serosa of the gall-bladder was edematous. No gall-stones were found. Lymph nodes around the hepatoduodenal area were enlarged and strikingly deep brown in color, and gave a positive iron stain. The pancreas was a deep ochre and its consistency was fibrotic. On section the normal lobular pattern was present. The gastrointestinal and genitourinary tracts were normal. The adrenals and thyroid were unremarkable. The testes were of normal size and shape and were boggy to palpation. Bone marrow had the usual deep red appearance.

On microscopic examination there was a diffuse moderate passive congestion of the lungs, with a few "heart failure" cells present. In some fields edema fluid was seen within the alveoli. The myocardium was diffusely and moderately fibrotic, with large fibrotic areas. There was marked deposition of hemosiderin in the cardiac fibers and in macrophages, particularly in the involved areas. The spleen was fibrotic and congested, with mild hemosiderin depositions. The liver was cirrhotic.

with marked bile duct proliferation, fatty metamorphosis and heavy deposition of hemosiderin in parenchymal and Kupffer's cells. The pancreatic connective tissue was also markedly increased, with much hemosiderin in the parenchymal cells, islet cells and stromal fibroblasts. Hemosiderin was also abundantly present in the zona glomerulosa of the adrenals, the mucosa of the stomach, the epithelial cells of the thyroid and parathyroid, the renal tubules and the cystic duct and peripancreatic lymph nodes.

Discussion

In Sheldon's classic monograph on hemochromatosis, myocardial failure is mentioned as an uncommon cause of death.[1] Within more recent years, several reports of hemochromatosis causing cardiac symptoms and death in congestive heart failure have appeared in the literature.[2-9] The French [13-16] have stressed this entity and have termed it an endocrino-hepato-cardiaque syndrome. It occurs almost exclusively in young adults and consists of the usual features of hemochromatosis with genital hypoplasia and heart failure. Bothwell and Alper [4] have reviewed the literature and have tabulated 33 cases of hemochromatosis in whom there was heart failure. Thirty-one of the 33 cases were males. Their conclusions were that the cardiac signs and symptoms were variable, and that once the cardiac symptoms appeared, these patients uniformly had a poor prognosis, the average survival time being less than one year. These patients responded poorly to digitalis therapy. In most of the cases there was an associated arrhythmia, with extrasystoles the disturbance most frequently seen. Most of the cases with myocardial damage terminated fatally in congestive failure, the average age at death being 38. The electrocardiograms were indefinite, but in most cases there was evidence of myocardial damage, while others had arrhythmias. Another frequent feature has been the occurrence of low voltage in the tracings.

Keschner [2] states that since the discovery of insulin the life span of patients with hemochromatosis has increased, and thus cardiac failure and "liver deaths" are now the major causes of death.

Many authors [1, 2, 13, 16] have stressed that there is a great disparity between the pathologic changes and the clinical evidence of cardiac derangement. Sheldon has stated: "Several cases have died from cardiac failure, but on the whole the extensive deposits of pigment laid down in this organ produce little evidence of their presence." Because of the lack of correlation between the extent of iron deposition in the myocardium and the presence of heart failure, endocrine factors have been invoked to explain this occurrence.[13-16] The nature of the dysfunction is rather obscure, but adrenal insufficiency has been incriminated.

Bothwell et al.,[3] using radioiron, have studied several cases. Their studies have tended to indicate that the damage to the myocardium was not related so much to the degree of iron deposition as to the rate at which it is laid down. This concept attempts to explain the discrepancy between the degree of iron deposition in the myocardium and the amount of discernible damage. Swan and Dewar [5] feel that the extensive changes in the heart muscle itself appear to be an adequate explanation of the heart failure.

In attempting to correlate the clinical and pathologic findings, one has to separate those cases who show only arrhythmias or electrocardiographic abnor-

malities which result from localized changes from those who show mechanical incompetence and in whom one should expect to find diffuse myocardial involvement.

Perhaps the situation is similar to the experimental one in dogs, where localized myocardial scarring by cautery resulted in arrhythmias but not heart failure, whereas generalized muscular damage caused by embolization of the coronary arteries has led to heart failure.[17]

This case had cardiac involvement with congestive heart failure. Electrocardiographically, there were low voltage and S-T segment and T wave changes. At some time during the course of the illness there were auricular fibrillation and a favorable response to digitalis. Microscopically there was a good correlation between the degree of fibrosis and the amount of hemosiderin deposits present in the cardiac muscle.

The etiology of the cardiac failure was not immediately discernible and, to clarify the problem, cardiac catheterization was performed. It is well known that patients with cirrhosis occasionally go into heart failure due to concomitant beriberi heart disease. This type of failure has a "high cardiac output."

At the time of catheterization, normal pressures, graphic contours and cardiac outputs were found. Therefore, at the time of the procedure, the patient was not in congestive failure, nor could he have been in a high output failure previously.

Summary

1. A case is presented of hemochromatosis with myocardial failure, typical electrocardiographic changes and a good response to digitalis.

2. Cardiac catheterization was performed and normal data were obtained. It is concluded that, in this case, a "high cardiac output" type of failure did not occur.

3. Microscopically, there was a good correlation between the degree of fibrosis and the amount of pigment deposition.

4. A review of clinical-pathologic concepts is presented.

Acknowledgment

I wish to thank Dr. Massimo Calabresi and Dr. Raymond B. Yesner for their helpful criticism.

Summario in Interlingua

Es presentate un caso de hemochromatosis del corde con disfallimento myocardial in que catheterisation cardiac esseva effectuate.

Un revista del litteratura revela que in le passato disfallimento myocardial esseva considerate como un causa de morte pauco commun. Tamen, in annos plus recente plure reportos de symptomas cardiac con morte in congestive disfallimento cardiac ha essite publicate. Le majoritate de iste casos concerneva masculos. Le responsa a digitalis non es bon. Le signos e symptomas cardiac es variabile. Le constatationes electrocardiographic non es definite. Si tosto que symptomas cardiac ha occurrite, le prognose deveni adverse con probabilitate de morte intra un anno. Le etate medie al tempore del morte es 38 annos. Le majoritate del electrocardiogrammas monstra affectiones del myocardio. Alteres monstra arrhythmia.

Multe autores ha signalate le disparitate inter le stato clinic e le stato pathologic. Pro explicar le absentia de correlation inter le occurrentia de disfallimento cardiac e le grado de deposition de ferro in le myocardio, plure autores ha citate factores endocrin, durante que alteres crede plus tosto que non le grado sed le intensitate del deposition de ferro es significative.

In le caso del presente reporto, le patiente habeva disfallimento myocardial, alterationes electrocardiogrphic que esseva typic de morbo myocardial, fibrillation auricular, e un bon responsa a digitalis. Le catheterisation cardiac resultava in constatationes normal. Istos revelava que le patiente non suffreva del typo de disfallimento que es characterisate per "alte grados de rendimento cardiac." Le examine microscopic monstrava un bon grado de correlation inter le fibrosis e le deposition de pigmento.

BIBLIOGRAPHY

1. Sheldon, J. H.: Haemochromatosis, 1935, Oxford University Press, London.
2. Keschner, H. W.: The heart in hemochromatosis, South. M. J. **44**: 927–930, 1951.
3. Bothwell, T. H., van Lingen, B., Alper, T., and du Preez, M. L.: The cardiac complications of hemochromatosis, Am. Heart J. **43**: 333–340 (Mar.) 1952.
4. Bothwell, T. H., and Alper, T.: The cardiac complications of haemochromatosis, report of a case with a review of the literature, South African J. Clin. Sc. **2**: 226–238 (Sept.) 1951.
5. Swan, W. G. A., and Dewar, H. A.: The heart in hemochromatosis, Brit. Heart J. **15**: 117–124 (Jan.) 1952.
6. Tucker, H. St. G., Jr., Moss, L. F., and Williams, J. P.: Hemochromatosis with death from heart failure, Am. Heart J. **35**: 993–999 (June) 1948.
7. Petit, D. W.: Hemochromatosis with complete heart block, Am. Heart J. **29**: 253, 1945.
8. Horns, H. L.: Hemochromatosis. Cardiac failure associated with extensive hemosiderosis of the heart, Am. J. Med. **6**: 272–274 (Feb.) 1949.
9. Graef, I., Newman, W., and Olivett, R. G.: Cardiac manifestations of hemochromatosis, delivered before the American Heart Association meeting at Atlantic City, June, 1949.
10. Cournand, A., Riley, R. L., Breed, E. S., Baldwin, E., and Richards, D. W.: Measurement of cardiac output in man using the technique of catheterization of the right auricle or ventricle, J. Clin. Investigation **24**: 106, 1945.
11. Rappaport, M., and Sarnoff, S. J.: An electronic multi-range, multichannel, direct writing pressure recorder, Federation Proc. **9**: 33, 1950.
12. Peters, J. P., and Van Slyke, D. D.: Quantitative clinical chemistry, Vol. 2, 1932, The Williams and Wilkins Company, Baltimore.
13. Clerc, A., Bascourret, M., and Andre, R.: Pigmentary cirrhosis, testicular atrophy and grave cardiac insufficiency, Bull. et mém. Soc. méd. d. hôp. de Paris **51**: 1228, 1935.
14. De Gennes, L., Delarue, J., and de Véricourt, R.: Pigmentary cirrhosis, testicular atrophy and cardiac insufficiency (endocrinocardiac syndrome), Bull. et mém. Soc. méd. d. hôp. de Paris **51**: 1008, 1935.
15. de Véricourt, R.: Le syndrome endocrino-hépato-myocardiaque, 1936, Masson, Paris.
16. Oumansky, V., and Longuet, A.: Le syndrome endocrino-cardiaque, Presse méd. **46**: 388, 1938.
17. Roos, A., and Smith, J. R.: The production of experimental heart failure in dogs with intact circulation, Am. J. Physiol. **153**: 558, 1948.

THROMBOHEMOLYTIC THROMBOCYTOPENIC PURPURA AND LUPUS ERYTHEMATOSUS *

By Bernard M. Siegel, M.D., *Sepulveda, California,* Irving A. Friedman, M.D., *Chicago, Illinois,* Samuel Kessler, M.D., *Paterson, New Jersey,* and Steven O. Schwartz, M.D., F.A.C.P., *Chicago, Illinois*

Clinicians have become increasingly alert to a syndrome characterized by the association of hemolytic anemia, thrombocytopenia and neurologic manifestations, first described by Moschcowitz [1] and recently extensively reviewed by Singer.[2] The number of cases reported has increased in proportion to growing awareness.

The term "thrombotic thrombocytopenic purpura" is in popular use for this syndrome,[3] although a somewhat more descriptive name, "thrombohemolytic thrombocytopenic purpura," has also been proposed.[4]

In the reported cases the course is always said to have been fulminating and downward from the time of the clinical appearance of the diagnostic triad; however, reëxamination of the tissues of patients who later presented clinically diagnostic symptoms often suggests that the pathologic process may have been chronic and have antedated the appearance of typical symptoms.

Recently we had an opportunity to study a woman who, clinically and histologically, had had classic thrombohemolytic thrombocytopenic purpura but who has had a complete clinical remission for 15 months since the onset of acute symptoms. She had been treated with steroids and by splenectomy, following which a positive L. E. phenomenon developed.

Case Report

History: A 29 year old Negro woman was admitted to Cook County Hospital on October 12, 1954, with a history of headache followed by a generalized convulsive seizure, during which she was reported to have been incoherent. Another seizure occurred on the day before admission and was associated with vomiting and the onset of slurred speech.

Significant history was later obtained from the Medical Branch of the University of Texas, where the patient was seen on several occasions from June 7 to July 24, 1954. She had had transient episodes of severe bitemporal headache, "thick" tongue, fainting and crying spells, sleep disturbance and suicidal ideas. Symptomatic therapy with Dexamyl and elixir phenobarbital gave improvement. An impression of depressive reaction or conversion reaction, or both, was made.

Physical Examination: On admission to Cook County Hospital the patient was acutely ill, pale and disoriented. The sensorium was clouded. She spoke with a slow mouthing of words and slurred speech, and made occasional erratic, purposeless, nonathetoid movements of the hands. Strange facial grimaces, which were inappropriate to the situation, were accompanied by episodes of sobbing and crying.

* Received for publication April 21, 1956.

From the Hematology Laboratory and the Hektoen Institute for Medical Research of the Cook County Hospital, Chicago.

Supported by grants from the Olivia Sue Dvore, Edward Friedman and Benjamin Fishbain Foundations.

Requests for reprints should be addressed to Steven O. Schwartz, M.D., 637 South Wood Street, Chicago 12, Illinois.

The blood pressure was 100/68 mm. of Hg; respirations were 16 per minute. Temperature was 101.8° F. by rectum. The sclerae were yellow and the conjunctivae pale. Petechiae were observed on the right conjunctiva, the tip of the tongue, and over the trunk and the extremities, as were a few small, soft, discrete, nontender cervical and axillary nodes. A soft systolic murmur was heard all over the precordium. The spleen was not palpable. The cranial nerves were intact. Bilateral positive Babinski's, Gonda's, Gordon's and Oppenheim's responses were present.

Laboratory Studies: In the initial laboratory studies the red blood cell count was 1.42 million; hemoglobin, 28% (4.3 gm.); white blood cell count, 8,100. No platelets were seen on the blood film. There were 39 neutrophils, 30 bands, 1 metamyelocyte, 20 lymphocytes and 10 monocytes, and 14 nucleated red blood cells per hundred white blood cells. The red cells exhibited moderate anisocytosis, poikilocytosis and polychromatophilia. There was moderate toxicity of the white cells. Platelets numbered 8,500, and the reticulocyte count was 33.1%. Bleeding time was prolonged, the ear puncture still bleeding almost 20 hours later; clotting time, 12 minutes 15 seconds, with no clot retraction in five hours; prothrombin time, 13 seconds; prothrombin consumption reduced.

Urinalysis of a catheterized specimen read: specific gravity, 1.020; acid reaction; 4 plus albuminuria; no sugar or acetone; 2 plus urobilinogen; 1 or 2 red blood cells and occasional granular casts per low power field.

Marrow obtained by sternal puncture was moderately hypercellular. Megakaryocytes were present and appeared normal. The nucleated red blood cell: white blood cell ratio was approximately 1:1. Erythropoiesis was normoblastic, granulopoiesis intact. There was a slight increase in reticulum cells and lymphocytes. Both direct and indirect Coombs' tests gave negative results. Cold agglutinins were found in the following titers: saline, 1:256; albumin, 1:128; papain, 1:1024. A lupus erythematosus preparation was negative.

The total protein on admission was 8.4 gm.%, with 3.8 gm.% albumin and 4.6 gm.% globulin. The inorganic phosphorus was 5.0 mg.%. The nonprotein nitrogen, chloride, sodium, potassium, total cholesterol and alkaline phosphatase values were within normal limits. Cephalin flocculation was 1 plus; thymol turbidity, 8.4 units; gamma globulin, 1.60 gm.%. The icterus index was 31, with a total serum bilirubin of 2.8 mg.% and an indirect reaction of 2.4 mg.%. Spinal puncture disclosed an opening pressure of 220 mm. water, with clear fluid; glucose, 91 mg.%; protein, 54 mg.%; chlorides, 115 mg.%; Pandy, 2 plus. A colloidal gold curve was obtained —5511100000—but was reported by the laboratory as unsatisfactory. Results of the blood Kahn test and spinal fluid Wassermann test were negative. A mucoprotein determination was 155 mg.%.

The chest roentgenogram showed normal-appearing lung fields, and four views of the skull were normal. Two cultures of blood, as well as urine and cerebral spinal fluid cultures, were negative. The electrocardiogram disclosed a sinus arrhythmia with low voltage in the standard leads.

A clinical diagnosis of thrombohemolytic thrombocytopenic purpura was made.

Biopsies: Biopsy of the left gastrocnemius muscle was done. A few lymphocytes and plasma cells surrounded small capillaries without apparent changes in the capillary wall. The endothelium of the interstitial vessels was slightly swollen. An atrophic epidermis and an edematous dermis were reported on skin biopsy. The small blood vessels seen in the section were acellular. The findings were suggestive but not diagnostic of thrombohemolytic thrombocytopenic purpura.

Treatment and Course: The patient was treated with antibiotics, blood and intravenous fluids; 40 units of ACTH were administered in the intravenous glucose solution over an eight to 10 hour period for the first two hospital days, and 30 units

on the third hospital day. No response in platelets was noted. Steroid therapy was continued, 300 mg. of cortisone a day in divided doses. The icterus index remained elevated. Because of failure to respond to conservative treatment, splenectomy was advised. The patient was transferred to a surgical service 17 days after admission. She still had a somewhat clouded sensorium, and Babinski plantar responses were still present. On the day splenectomy was performed, hemoglobin was 81% (12.6 gm.), and the red blood cells were 4.19 million, with a reticulocyte count of 3.6%.

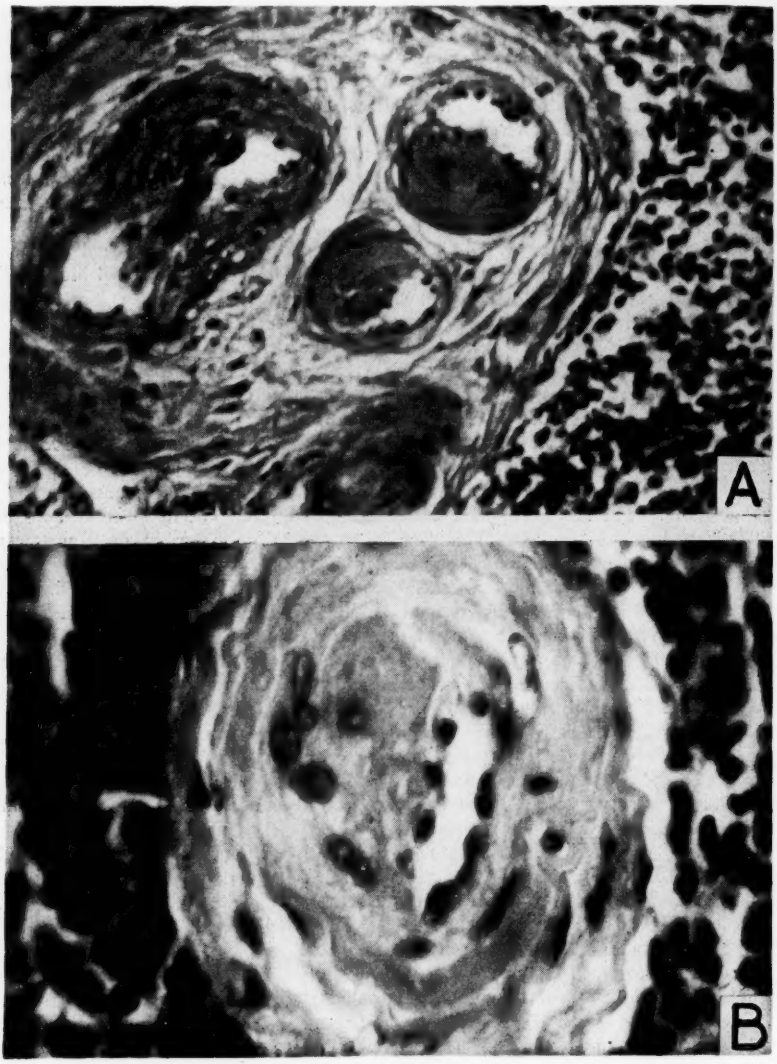


FIG. 1. Representative lesions in the spleen of the patient, demonstrating characteristic acellular material in the vessel walls (A and B).

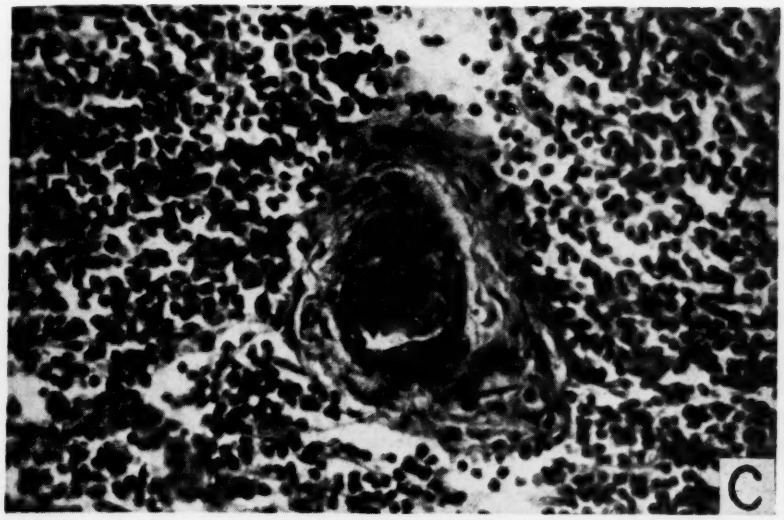


FIG. 1 C. Intravascular thrombus.

The patient had received cortisone and multiple transfusions prior to surgery. Steroids were continued throughout the immediate postoperative period. The dosage was slowly reduced, so that by the eighth postoperative day cortisone had been completely withdrawn. By the third postoperative day, mental clearing and improved orientation were evident. A platelet count on the first postoperative day was 245,000; the second, 257,000; the third, 145,000, with 1.5% reticulocytes; the fifth, 312,000; the seventh 280,000 with reticulocytes, 0.9%. On the ninth day after operation, bleeding time was 2 minutes 45 seconds; prothrombin time, 14 seconds (75%); coagulation time, 10 minutes 30 seconds; prothrombin consumption, normal.

Characteristic lesions of thrombohemolytic thrombocytopenic purpura (figure 1) were identified in microscopic sections of the spleen prepared with hematoxylin-eosin and periodic acid Schiff stains.

The patient was returned to the medical service 15 days after splenectomy, well oriented, with a positive right Babinski response. On the ward she was observed for changes in behavior or physical signs for six days, and was then discharged for follow-up care by the Hematology Clinic.

On January 3, 1955, the patient was admitted because of acute pyelonephritis, at which time she had an essentially normal hemogram and marrow. She responded to appropriate antibiotics and was discharged after 10 days.

On January 18 an L. E. cell preparation (clot method) was negative, and all hematologic values were in the normal range. On June 1 an L. E. cell preparation was found to be positive, and when repeated on July 6 was again found positive. At that time the following serum values were obtained: total protein 8.1 gm.%; albumin, 5.4 gm.%; globulin, 2.7 gm.%; gamma globulin, 1.45 gm.%; cephalin flocculation, 0; thymol turbidity, 5.7 units. A scalene fat pad biopsy revealed vessels in the fat tissue which appeared normal. Lymph node tissue was not obtained in the specimen.

COMMENTS

The patient whose case is reported presented a striking association of severe hemolytic anemia, thrombocytopenia with purpura, and neurologic involvement

manifested by psychotic behavior and abnormal reflexes. The clinical diagnosis of thrombohemolytic thrombocytopenic purpura seemed justified. The clinical impression was strengthened by a history of an antecedent four month period of mental disturbance. Some reports in the literature record that the patients were first treated as psychiatric problems.[5] The neuropathy of this syndrome is characterized by an almost exclusive involvement of the gray matter of the brain,[6, 7] with waxing and waning of neurologic symptoms, as was noted in our case, both historically and during the observation period.

Biopsies of the skin and gastrocnemius muscle were obtained. One of the histologic sections of the skin suggested thrombohemolytic thrombocytopenic purpura, but on review the evidence was not diagnostic.

Lupus erythematosus disseminata is known to be able to produce hemolytic anemia, thrombocytopenia and central nervous system involvement. Idiopathic thrombocytopenic purpura could present these symptoms and signs. Our records contain such a case, clinically diagnosed as Moschcowitz's disease, which on tissue examination showed only thrombocytopenic purpura. Lymphoma was considered in the differential diagnosis, but neither the clinical nor the laboratory findings prior to splenectomy supported that diagnosis.

As early as 1939 Gitlow and Goldmark [8] considered a relationship of this disease process to lupus erythematosus disseminata. The work of Gore [9] and Orbison [10] has well demonstrated that the micropathologic lesions in thrombohemolytic thrombocytopenic purpura are vascular and not associated with perivascular cellular reaction. Symmers and Gillett [11] reported a case in which the vascular changes were those of polyarteritis nodosa; the "wire-loop" glomeruli and perivascular "onion-skin" lesions those of lupus; and, finally, there was the typical lesion of thrombohemolytic thrombocytopenic purpura. Laszlo and his co-workers [12] have reported the lesions of thrombohemolytic thrombocytopenic purpura on postmortem examination, although the clinical diagnosis had been lupus, with a positive L. E. cell preparation. Beigelman,[13] as well as Gendel and collaborators,[14] has also published reports of the lesions of lupus associated with those of thrombohemolytic thrombocytopenic purpura. A high incidence of allergic phenomena in such cases was noted by Adelson and his colleagues.[4] Barondess [15] also accepted the possibility that this process represented a collagen disease, and suggested that a further trial of steroids and splenectomy was indicated.

Ours is the first report of the presence of the L. E. cell phenomenon in a patient who clinically suggested a diagnosis of thrombohemolytic thrombocytopenic purpura, and in whom the diagnosis was histologically confirmed during life.

We do not interpret the presence of the L. E. cell phenomenon in this case as necessarily indicating the presence of a distinctive disease process called lupus erythematosus. On the other hand, the presence of the L. E. cell in most cases is accompanied by either the clinical or the pathologic manifestations of lupus. In a recent study,[16] the L. E. cell has been found in classical rheumatoid arthritis. The L. E. cell has also been reported in polyarteritis nodosa [17] and dermatomyositis,[18] with penicillin sensitivity reactions,[19] and with Butazolidin therapy.[18] The phenomenon [20–24] has also accompanied a "collagen disease" syndrome occurring in patients having hydralazine therapy. Beigelman [13] thought of thrombohemo-

lytic thrombocytopenic purpura as a variation of the "collagen diseases," the clinical appearance being determined by the location of the hyperergic reactive tissue. This concept appears to be gaining acceptance. The findings of the L. E. cell phenomenon in our patient indirectly lends further validity to this concept. Only in a few cases has the phenomenon been reported [25] present when some hyperergic or "collagen disease" process was not demonstrably or strongly suggested. In the present case it is considered to be a laboratory reflection of a basically hyperergic pathologic process.

In the reported cases of this condition the course had been rapidly downhill from the time of the appearance of the characteristic clinical triad. In the two cases accepted by Singer [2] as examples of remission the patients presented only hemolytic anemia. Splenectomy was performed in both cases. The patients later presented more characteristic clinical manifestations preterminally. The poor prognosis in our case was evident, and the failure to produce remission in the reported cases of splenectomy during this clinical phase of the disease was known. Splenectomy was considered justified, however, because (1) the clinical characteristics might have been secondary manifestations of one of the diseases considered in the differential diagnosis; (2) steroids had not been previously used to control the bleeding tendency and hemolytic anemia prior to splenectomy in thrombohemolytic thrombocytopenic purpura; (3) there is still some question as to the value of splenectomy in thrombohemolytic thrombocytopenic purpura.

The administration of steroids reduced the hemorrhagic tendency and ameliorated the hemolytic process to a degree that allowed an adequate hemoglobin and red blood cell level to be built up prior to surgery. Splenectomy was performed without incident. Following splenectomy, clinical improvement was rapid and almost complete. Steroids were withdrawn without recurrence of purpura or hemolytic anemia; the sensorium cleared in a few days.

As of this writing, 15 months after first admission, the patient remains entirely asymptomatic and has a normal hemogram. Peripheral reflex abnormalities are the only detectable residua of the initial attack.

Summary and Conclusions

A 29 year old Negro woman presented a classic triad of hemolytic anemia, thrombocytopenic purpura and bizarre neurologic manifestations, leading to the clinical diagnosis of thrombohemolytic thrombocytopenic purpura. She was critically ill and the immediate prognosis was grave. The patient received steroids and was subjected to splenectomy. The diagnosis was confirmed on histologic examination of the spleen. Rapid improvement was observed postoperatively; the patient has maintained complete clinical and hematologic remission for 15 months. The L. E. cell phenomenon was elicited seven months after splenectomy.

Among the reported cases of this syndrome, evidence has been presented that the disease process can exist in a chronic form and is not always an acute fulminant disease. For that reason, we cannot interpret the effect of steroids and splenectomy as necessarily curative in our case. We can, however, urge that a more active therapeutic approach be adopted toward thrombohemolytic

thrombocytopenic purpura, in an attempt to produce remission through the use of steroids and splenectomy.

In view of current concepts of the pathogenesis of thrombohemolytic thrombocytopenic purpura, our findings raise questions that may prove significant:

1. Have we added further evidence of a common etiologic background of thrombohemolytic thrombocytopenic purpura and lupus erythematosus?

2. Considering our patient's response to therapy, can one expect a prolonged remission or even a termination of this disease process by steroid therapy and splenectomy?

Addendum

The patient remains in clinical remission at the time of publication of this report, approximately 32 months after the onset of her illness.

Summario in Interlingua

Un femina negre de 29 annos de etate presentava le symptomas de anemia hemolytic e purpura thrombocytopenic con le manifestationes neurologic de mal de capite, accessos de perdita de conscientia, convulsiones generalisate, incoherentia, vomito, enunciation diffuse, e disturbationes emotional de un duration de quatro menses. Le diagnose clinic esseva purpura thrombocytopenic thrombohemolytic. Le patiente esseva criticamente malade, e le prognose esseva grave. Post un periodo de essayo con therapia steroide (que esseva de valor in subjugar le tendentia hemorrhagic e meliorar le processo hemolytic), splenectomia esseva effectuate. Le diagnose esseva confirmate per un examine histologic del splen. Le subsequente melioration esseva remarcabile tanto clinica-como etiam hematologicamente. Le remission ha essite mantenite durante 15 menses. Septe menses post le splenectomia, le phenomeno de L.E. esseva producite.

Le diagnose differential se preoccupava de purpura thrombocytopenic thrombohemolytic, lupus erythematose, purpura thrombocytopenic idiopathic, e lymphoma. Le intime relation de purpura thrombocytopenic thrombohemolytic con lupus erythematose, specialmente con respecto al histologia vascular, ha previemente essite signalate, sed isto es le prime reporto del presentia del phenomeno de L.E. in un vive patiente con le diagnose clinic e histologic de purpura thrombocytopenic thrombohemolytic. Le signification del phenomeno de L.E. in iste patiente jaceva in le facto que illo poteva esser interpretate como un reflexion laboratorial de un processo pathologic de character fundamentalmente hyperergic. Es digne de nota que le phenomeno de L.E., excepte in rar casos, ha essite reportate solmente in le presentia demonstrate o suspecte de un morbo hyperergic o "collagenic."

Le presente reporto supporta le concepto que purpura thrombocytopenic thrombohemolytic pote sequer un curso chronic plus tosto que un acute curso fulminante. Per consequente, effortios energic debe esser facite a effectuar un remission per medio de therapia steroide o splenectomia. Nostre constatationes etiam signala le possibilitate que il existe un commun base etiologic pro purpura thrombocytopenic thrombohemolytic e lupus erythematose.

BIBLIOGRAPHY

1. Moschcowitz, E.: An acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries; an undescribed disease, Arch. Int. Med. **36**: 89–93, 1925.
2. Singer, K.: Thrombotic thrombocytopenic purpura, *in* Advances in internal medicine, 1954, The Year Book Publishers, Chicago, pp. 195–234.
3. Singer, K., Bornstein, F. P., and Wile, S. A.: Thrombotic thrombocytopenic purpura: hemorrhagic diathesis with generalized platelet thrombosis, Blood **2**: 542–554, 1947.

4. Adelson, E., Heitzman, E. J., and Fennessey, J. F.: Thrombohemolytic thrombocytopenic purpura, Arch. Int. Med. **94**: 42–60, 1954.
5. Goldenberg, P. T., Thayer, J. E., and Hastings, L. P.: Febrile thrombopenic purpura with hemolytic anemia and platelet thrombosis, New England J. Med. **243**: 252–256, 1950.
6. Adams, R. D., Cammermeyer, J., and Fitzgerald, P. J.: The neuropathological aspects of thrombocytic acroangio-thrombosis, J. Neurol., Neurosurg. and Psychiat. **11**: 27–43, 1948.
7. Wyatt, J. P., and Lee, R. S.: Hemorrhagic encephalopathy due to disseminated thrombocytic thrombosis, Arch. Path. **49**: 582–589, 1950.
8. Gitlow, S., and Goldmark, C.: Generalized capillary and arteriolar thrombosis, Ann. Int. Med. **13**: 1046–1067, 1939.
9. Gore, I.: Disseminated arteriolar and capillary platelet thrombosis, Am. J. Path. **26**: 155–166, 1948.
10. Orbison, J. L.: Morphology of thrombotic thrombocytopenic purpura with demonstration of aneurysms, Am. J. Path. **28**: 129–143, 1952.
11. Symmers, W. St. C., and Gillett, R.: Polyarteritis nodosa associated with malignant hypertension, disseminated platelet thrombosis, "wire-loop" glomeruli, pulmonary silico-tuberculosis, and sarcoidosis-like lymphadenopathy, Arch. Path. **52**: 489–504, 1951.
12. Laszlo, M. H., Alvarez, A., and Feldman, F.: The association of thrombotic thrombocytopenic purpura and disseminated lupus erythematosus: report of a case, Ann. Int. Med. **42**: 1308–1320, 1955.
13. Beigelman, P. M.: Variants of the platelet thrombosis syndrome and their relationship to disseminated lupus, Arch. Path. **51**: 213–223, 1951.
14. Gendel, B. R., Young, J. M., and Krauss, A. P.: Thrombotic thrombocytopenic purpura, Am. J. Med. **13**: 3–11, 1952.
15. Barondess, J. A.: Thrombotic thrombocytopenic purpura, Am. J. Med. **13**: 294–310, 1952.
16. Friedman, I. A., Sickley, J. F., Poske, R. M., Black, A., Bronsky, D., Hartz, W. H., Jr., Feldhake, C., Reeder, P. S. and Katz, E. M.: The L. E. phenomenon in rheumatoid arthritis, Ann. Int. Med. **46**: 1113–1136, 1957.
17. Lincoln, M., and Ricker, W. A.: A case of periarteritis nodosa with L. E. cells. Apparent complete remission with cortisone therapy, Ann. Int. Med. **41**: 639–646, 1954.
18. Ogryzlo, M. A.: The L. E. (lupus erythematosus) cell reaction: its morphology and specificity, Annual Meeting of American Rheumatism Association, June 3, 1955, Abstract No. 6 in Bull. Rheumat. Dis. **6**: 94, 1955.
19. Walsh, J. R., and Zimmerman, H. J.: The demonstration of the L. E. phenomenon in patients with penicillin hypersensitivity, Blood **8**: 65–71, 1953.
20. Dustan, H. P., Taylor, R. D., Corcoran, A. C., and Page, I. H.: Rheumatic and febrile syndrome during prolonged hydralazine treatment, J. A. M. A. **154**: 23–29, 1954.
21. Perry, H. M., Jr., and Schroeder, H. A.: Syndrome simulating collagen disease caused by hydralazine (Apresoline), J. A. M. A. **154**: 670–673, 1954.
22. Reinhardt, D. S., and Waldron, J. M.: Lupus erythematosus-like syndrome complicating hydralazine (Apresoline) therapy, J. A. M. A. **155**: 1491–1492, 1954.
23. Shackman, N. H., Swiller, A. I., and Morrison, M.: Syndrome simulating acute disseminated lupus erythematosus: appearance after hydralazine (Apresoline) therapy, J. A. M. A. **155**: 1492–1494, 1954.
24. Henn, M. J., Parkin, T. W., Hargraves, M. M., and Odel, H. M.: Acute systemic lupus erythematosus syndrome from hydralazine hydrochloride, Arch. Int. Med. **95**: 857–862, 1955.
25. Berman, L., Axelrod, A. R., Goodman, H. L., and McClaughry, R. I.: So-called lupus erythematosus inclusion phenomenon of bone marrow and blood, Am. J. Clin. Path. **20**: 403–418, 1950.

Q FEVER: REPORT OF A CASE SIMULATING LYMPHOMA*

By HAROLD S. RAMOS, Captain (MC), U.S.A.F., ROBERT E. HODGES, Captain (MC), U.S.A., and WILLIAM H. MERONEY, Lt. Col. (MC), U.S.A., *Washington, D. C.*

DERRICK [1] in 1937 reported nine cases of a new clinical entity in Queensland, Australia, which he designated as "Q fever." Burnet [2] isolated the etiologic agent in these cases and correctly identified it as a rickettsia. Until recently, most physicians have considered this disease little more than a medical curiosity, and one of importance only in Australia and in the western areas of the United States. It has become increasingly apparent that this is a widespread disease entity found in many sections of the United States and most countries of the world.[3] Many cases of Q fever are unrecognized because of lack of appreciation of the cosmopolitan nature of the infection and the varied symptomatology that it can produce. The present report is of a case in a nonendemic area which initially simulated an acute lymphomatous process.

CASE REPORT

A 19 year old Negro man was admitted to Walter Reed Army Hospital on November 1, 1955, complaining of abdominal pain, nausea and vomiting, dark urine, chills, and fever of 24 hours' duration. He had been hospitalized in a military hospital in Texas from August 11 to October 10, 1955, for infectious hepatitis. Except for mild fatigability, he had had no symptoms from late September until the onset of the present illness. He had been on leave in Washington, D. C., for 15 days when, on October 29, 1955, he developed an aching pain across the lower part of his back and in the right upper quadrant of the abdomen. On October 30 he was seen at a dispensary, where he was given symptomatic treatment which gave him temporary relief. That evening he had headache, pain on motion of the eyes, shaking chills and feverishness. The following day he felt much improved until evening, when he had nausea, vomiting, epigastric distress, shaking chills, feverishness, and a mild, nonproductive cough. At this time he noted that his urine was dark in color. On November 1 he was admitted to Walter Reed Army Hospital.

During his leave in Washington the patient had visited a farm in Upper Marlboro, Maryland. There were no livestock on this farm, but there were some in the immediate neighborhood. Immediately prior to this time he had been stationed in Texas, in an area where cattle and sheep were grazed. It is of note that there were heavy dust storms in Texas during July and August, 1955. He denied any other association with livestock, and could not recall drinking raw milk.

The patient had been born in Washington, D. C., and had remained in this area prior to entering the military service. His military service had been spent in Texas, and he had visited Mexico on two one-day trips during June and July, 1955.

He had been in good health prior to contracting infectious hepatitis in August, 1955. A chest film taken during the first week in October, 1955, had been normal. His only previous illness had been a gonococcal urethritis in 1953, which responded

* Received for publication June 11, 1956.

From the Section of Metabolism, Department of Medicine, Walter Reed Army Hospital, Walter Reed Army Medical Center, Washington, D. C.

Requests for reprints should be addressed to Harold S. Ramos, Captain (MC), U.S.A.F., Walter Reed Army Hospital, Walter Reed Army Medical Center, Washington 12, D. C.

to penicillin. The review of systems revealed only a tendency to tire easily since the hepatitis. His parents were living and well, and there was no history of familial diseases.

Physical examination on admission revealed a well developed, well nourished 19 year old Negro who was alert and coöperative but appeared acutely ill. The height was 66 inches; weight, 165 pounds; temperature, 100° F., blood pressure, 120/80 mm. of Hg; pulse, 80. The sclerae were "muddy" but not jaundiced. The lungs were clear to percussion and auscultation, and the chest expanded symmetrically.

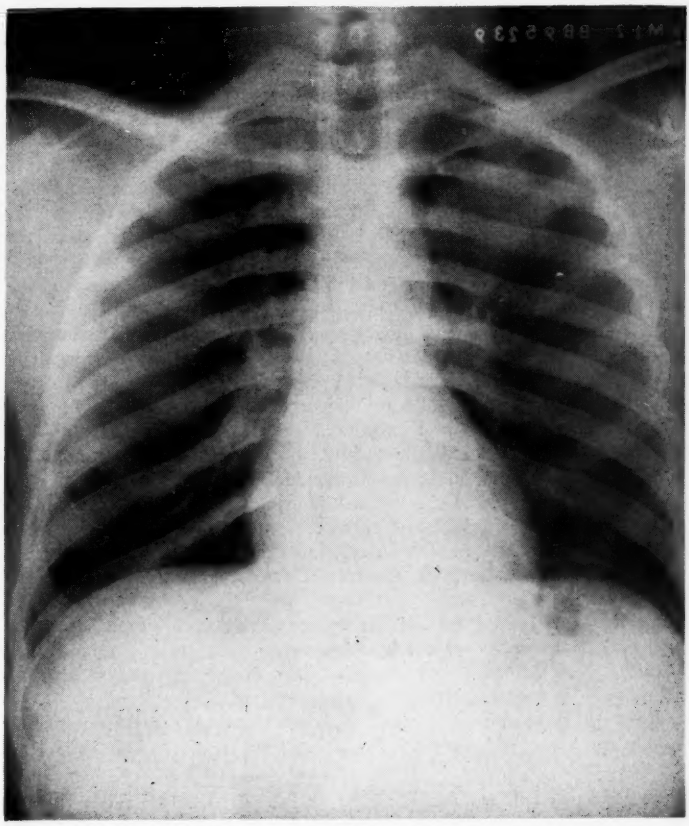


FIG. 1. Chest x-ray on admission, with the circumscribed infiltration in the left upper lung.

The heart was not enlarged or overactive, there was regular sinus rhythm, and no murmurs were heard.. The abdomen was tender in both upper quadrants. The liver was palpable 2 cm. below the right costal margin and was mildly tender. The spleen was palpable 8 cm. below the left costal margin and was exquisitely tender. The genitalia were normal. The cervical lymph nodes were small, shotty and nontender. The inguinal nodes were moderately enlarged, nontender and freely movable. Nodes in the axillae were 2 cm. in size and extremely tender. Neurologic examination was within normal limits.

At the time of admission a urinalysis revealed a specific gravity of 1.021 and an occasional white cell, but no albumin, sugar or bile. Peripheral blood examination revealed a hemoglobin of 10.8 gm./100 c.c.; hematocrit, 39%; leukocyte count, 5,600, with 58% neutrophils and 42% lymphocytes; corrected sedimentation rate (Wintrobe), 27; reticulocytes, 2.5%. Initially, the total serum bilirubin was 1.70 mg./100 c.c.; one-minute bilirubin, 0.35 mg./100 c.c.; thymol turbidity, 1.2 units; cephalin flocculation, negative. Blood cultures, stool cultures for typhoid and salmonella, febrile agglutinations for typhoid and brucellosis, and lupus erythematosus cell preparations were negative. Initial chest x-rays revealed a circular density 6 to 7 cm. in diameter in the left upper lung field which was well circumscribed and of ground-glass appearance. There was questionable enlargement of the mediastinal nodes draining this area (figure 1). X-rays of the abdomen showed marked splenomegaly and moderate hepatomegaly. There was bowing of the psoas muscle shadows, which suggested retroperitoneal node enlargement.

On the evening of admission the patient appeared extremely ill and his temperature rose to 105° F. Malaria smears taken at the height of the fever were negative. The patient vomited clear greenish fluid. Despite salicylate therapy the fever continued for six days, with spikes from 102° to 105° F. On the third hospital day a bone marrow aspiration revealed moderate hypocellularity, abundant megakaryocytes, and an increase in reticulum cells which were thought by the hematologist to be differentiating toward granulocytes. The erythroid-myeloid ratio was 1:2, and maturation was normal.

On the fourth hospital day a biopsy specimen taken from an enlarged axillary node showed nonspecific lymphadenitis. A gastrointestinal series revealed marked displacement of the stomach to the right by the enlarged spleen, but no other abnormality. The patient was maintained on intravenous fluids and received no antibiotics, but he began to improve after the fourth day.

By the seventh hospital day the patient was afebrile and asymptomatic, except for thrombophlebitis of the left forearm incident to an infiltration of intravenous fluids. A repeat film of the chest showed no significant change in the lesion. At this time the first of a series of blood specimens was drawn for Q fever complement fixation titer. Complement fixation titers for Q fever were 1:80, 1:320, 1:320, 1:640 and 1:1280 on the seventh, fourteenth, twenty-first, twenty-eighth and fifty-sixth hospital days, respectively.

During the convalescent period the splenomegaly and lymphadenopathy began to regress, and three weeks after admission the splenic tip could be palpated only with difficulty. The infiltration in the upper lobe of the left lung cleared gradually. During this period a moderate lymphocytosis appeared.

From the third to the fifth week of hospitalization several complications developed. On the eighteenth hospital day the patient began to complain of pain and swelling in his right hand, left wrist and left ankle. There was some swelling of the left wrist but no local heat or erythema. X-rays were negative. Examination of the stools for occult blood (guaiac), which had been negative initially, now became strongly positive. Efforts to determine the source of the bleeding, including barium enema studies with air contrast technic, were unsuccessful, and the bleeding ceased spontaneously within two weeks. On the thirtieth hospital day the patient complained of pain in the left calf, which was found to be tender in the region of the long saphenous vein. Symptomatic therapy was given for these complications, with gradual alleviation of the symptoms.

The patient was sent on convalescent leave, during which time he had no symptoms. Physical examination on his return to the hospital was normal. Chest films at this time showed a faint residual of the infiltrate in the left upper lobe. He was discharged to duty on January 16, 1956, 77 days after the onset of the illness.

Discussion

Q fever is an acute rickettsial disease, characterized by a sudden onset of headache, chills, fever, and variable respiratory symptoms. Retro-orbital pain and pain of the eye muscles on motion are frequent symptoms. The patient may complain of stiff neck, sore and aching joints, nausea, vomiting or diarrhea. The etiologic agent is *Coxiella burnetti,* and the common mode of transmission is inhalation of contaminated dust particles. Sheep, cattle and goats form the reservoir for most human infections.[3-5] The average incubation period is from 10 to 20 days, with an extreme range of from five days to five weeks. The disease is characterized by a remittent fever which may last from a few days to several weeks, but averages eight to 12 days. There is a relative bradycardia, with the pulse rarely over 100, even in the febrile phase. Splenomegaly has been reported in Q fever, although it is not an invariable finding.[6-9] These features were well illustrated in our patient (figure 2). There is a notable paucity of

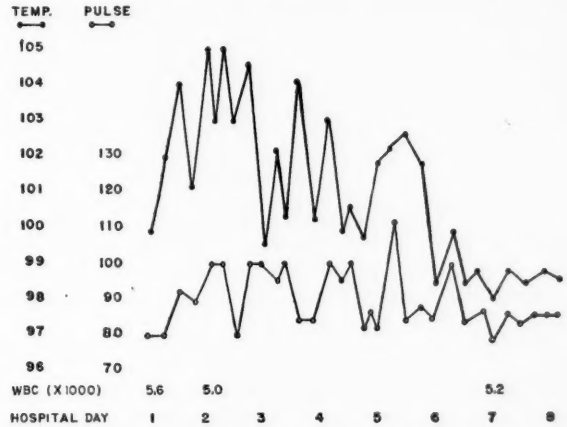


Fig. 2. Graphic record of temperature and pulse, illustrating relative bradycardia characteristic of Q fever.

physical findings. On x-ray the usual lesion is a homogeneous consolidation, which may be segmental or lobar, in the lower or midlung fields. Lesions similar to those of the present case have been reported but are relatively uncommon.[10]

There are few distinctive historical or physical features of Q fever, and the wide variety of complications may present confusing clinical problems. Arthritis, epididymitis, esophagitis and intestinal hemorrhage [7, 11, 12] have been reported, and as many as 25% in one series manifested a severe, transitory meningismus.[6] Germer and Schauber [13] reported the isolation of *C. burnetti* from the spinal fluid of one patient with Q fever meningitis.

Since the diagnosis depends upon the demonstration of a rising antibody titer in the patient's serum, or recovery of *C. burnetti* from the blood by animal inoculation, it is well to be acquainted with the atypical forms the disease may adopt. Although this is usually a self-limited disease with a mortality rate of less than 1% the complications can lead to prolonged morbidity, and in a small

number of severe cases sequelae develop. Recurrent attacks of fever, prolonged anorexia, swelling of the joints, pain in the back of the calves, and asthma may persist for several months.[6, 7, 9] Institution of proper therapy will reduce the acute morbidity and limit the development of sequelae. Terramycin provides prompt and effective treatment.[14–16]

The appearance of this patient on admission—with spiking remittent fever, anemia, axillary adenopathy, a large, tender spleen, a circumscribed lesion in the lung parenchyma, and a bone marrow showing increased reticulum cells—was suggestive of an acute lymphomatous process rather than an infectious one. Q fever complement fixation titers showed a rapid diagnostic rise, and the subsequent clinical course was consistent with Q fever. By that time, however, the patient had become afebrile and no specific therapy was given. Two of the common complications, arthritis and pain in the calves, developed in the convalescent phase. Occult blood in the stools suggested gastrointestinal hemorrhage, one of the reported complications, but no bleeding site could be found.

It was not possible to determine whether the infection was acquired in Texas, which is known to be an endemic area, or in the District of Columbia-Maryland areas, from which no previous cases of naturally occurring Q fever have been reported. The clinical and laboratory records of the previous hospitalization were reviewed and found to be consistent with a diagnosis of infectious hepatitis.

Summary

A case of Q fever with initial findings suggestive of an acute lymphomatous process has been presented and reviewed. Some of the common complications of Q fever have been discussed. It was not possible to discover the source of the infection in the present case, which appeared in a nonendemic area.

Summario in Interlingua

Febre de Queensland es un acute morbo rickettsial characterisate per un declaration subitanee de mal de capite, algor, febre, e variabile symptomas respiratori. Le agente etiologic es *Coxiella burnetii*, e le plus commun modo de inoculation consiste in le inhalation de contaminate particulas de pulvere. Le condition ha pauc characteristicas de alte specificitate, e le extense varietate de complicationes presenta frequentemente un problema clinic confuse. Es presentate e discutite un caso de febre de Queensland con characteristicas que resimila un acute processo lymphomatose.

Le patiente, un masculo negre de 19 annos de etate, esseva hospitalisate con le gravamines de febre, algor, disturbationes epigastric, nausea, e vomito. Al tempore del admission del patiente, su apparentia physic—con febre remittente a curso serrate, anemia, adenopathia axillar, un grande splen a sensibilitate sub pression, un lesion circumscripte in le parenchyma pulmonar, e augmento del cellulas reticular in le medulla ossee—suggereva un processo lymphomatose plus tosto que un condition infectiose. Le titro del fixation de complemento pro febre de Queensland revelava un rapide ascendita de signification diagnostic, e le subsequente curso clinic esseva de accordo con febre de Queensland. Duo del plus commun complicationes—arthritis e dolores in le suras—superveniva durante le phase reconvalescente.

Es signalate le importantia del correcte diagnose, proque le promptitude del tractamento pote reducer le grado de morbiditate e limitar le disveloppamento de sequellas. Terramycina se ha provate efficace in le therapia de febre de Queensland.

BIBLIOGRAPHY

1. Derrick, E. H.: "Q" fever, a new fever entity; clinical features, diagnosis, and laboratory investigations, M. J. Australia **2**: 281, 1937.
2. Burnet, F. M., and Freeman, M.: Experimental studies on the virus of "Q" fever, M. J. Australia **2**: 299, 1937.
3. Berge, T. O., and Lennette, E. H.: World distribution of Q fever: human, animal, and arthropod infection, Am. J. Hyg. **57**: 125, 1953.
4. Marmion, B. P.: Q fever: natural history and epidemiology of Q fever in man, Tr. Roy. Soc. Trop. Med. and Hyg. **48**: 197, 1954.
5. Clark, W. H., Lennette, E. H., and Romer, M. S.: Q fever in California. XI. An epidemiological summary of 350 cases occurring in Northern California during 1948–1949, Am. J. Hyg. **54**: 319, 1951.
6. Denlinger, R. B.: Clinical aspects of Q fever in Southern California: a study of eighty hospitalized cases, Ann. Int. Med. **30**: 510, 1949.
7. Dyer, R. E.: Clinical aspects of Q fever, Postgrad. Med. **2**: 392, 1952.
8. Fellers, F. X.: An outbreak of Q fever, U. S. Armed Forces M. J. **3**: 287, 1952.
9. Stoker, M. G. P.: Q fever: clinical features and laboratory diagnosis, Tr. Roy. Soc. Trop. Med. and Hyg. **48**: 191, 1954.
10. Jacobson, G., Denlinger, R. B., and Carter, R. A.: Roentgen manifestations of Q fever, Radiology **53**: 739, 1949.
11. Freygang, F.: Klinische, epidemiologische, und serologische Beobachtungen bei Q Fieber 1948–1949 in Nord-Wurttenberg, Deutsche med. Wchnschr. **74**: 1457, 1949.
12. Huebner, R. J., Jellison, W. L., and Beck, M. D.: Q fever—a review of current knowledge, Ann. Int. Med. **30**: 495, 1949.
13. Germer, W. D., and Schauber, W.: Q-fieber-meningitis in einem endemisch verseuchten Gebiet, Deutsche med. Wchnschr. **78**: 1209, 1953.
14. Ormsbee, R. A., Parker, H., and Pickens, E. G.: The comparative effectiveness of Aureomycin, Terramycin, chloramphenicol, erythromycin, and thiocymetin in suppressing experimental rickettsial infections in chick embryos, J. Infect. Dis. **96**: 162, 1955.
15. Frascarelli, R.: La febbre Q in Umbria: osservazioni cliniche su 51 casi con particolare riferimento al periodo di incubazione, alla funzionalita, epatica, agli anticorpi devianti il complemento ed alla precedente terapia con antibiotici, Riforma med. **66**: 197, 1952.
16. Giunchi, G.: La cura della febbre Q con la terramicina, Minerva med. **42**: 833, 1951.

EDITORIAL

CHELATION

In the class of compounds known as complexes, there is a group with special properties called chelates. The name chelate is derived from the Greek word for claw, an apt descriptive term for this type of substance. A chelate is a compound formed between a metallic ion and an organic molecule having two neighboring groups capable of simultaneously combining with the metal to form a ring structure. The chelate resembles a claw with the metal ion clutched between the pincers of the organic molecule.

The chelate structure has such high stability that the metal ion is no longer available for its usual reactions. Most of the biological, chemical, and physical properties of the metal are changed, e.g., solubility may be altered. Calcium oxalate is an insoluble chelate whereas calcium citrate is a soluble chelate. Tartrate or citrate is incorporated into the alkaline copper reagents, which are used for the determination of sugars, in order to convert the insoluble copper salts into water soluble chelates.

Although the principle of chelation had been used only sporadically in medical practice prior to the 1940s, it became of great importance early in World War II because of the danger of poisoning from the arsenic containing war gas, Lewisite. Peters,[1] in England, discovered that the mercapto groups of 2,3-dimercapto-1-propanol chelated the arsenic efficiently and tenaciously, yielding an inactive compound which could be readily eliminated. It was named British Anti Lewisite and is now known by its initials "BAL."

Shortly after the war the problem of atomic fission products led to the study of agents capable of decontaminating individuals or objects exposed to them. Many hitherto physiologically insignificant metals such as yttrium, strontium, uranium, plutonium and polonium have become important in medicine since they are either sources of atomic power or radioactive products of atomic fission.

Workers in Germany led by Pfeiffer and by Schwartzenbach had studied a series of compounds built upon a basic structure consisting of two carbon atoms and two nitrogen atoms, ethylene diamine. One compound in this series, ethylenediaminetetracetic acid, showed outstanding ability to chelate heavy metals, and is probably the most potent chelating agent known.

Chelates of ethylenediaminetetracetic acid (EDTA) with heavy metals are very stable and have remarkable properties, e.g., salts of lead, which are insoluble under alkaline conditions, are readily dissolved by EDTA.

Another property of chelates is important. Chelated metals may be displaced by other metals provided the second metal is bound more strongly

[1] Peters, R. A., Stocken, L. A., and Thompson, R. H. S.: British Anti Lewisite (BAL), Nature **156**: 616, 1945.

than the first. By proper manipulation of experimental conditions a series of metals can be described which will replace each other in ascending order. The ascending order of some of the metals of biological interest is usually as follows: Mg^{++}, Mn^{++}, Fe^{++}, Zn^{++}, Co^{++}, and Cu^{++}.[2] This means that a chelated metal in the earlier part of the list can be replaced by a metal occurring later.

The ability of EDTA to solubilize heavy metals can be used to advantage in dissolving calcific corneal opacities,[3] possibly in decalcifying areas of metastatic calcification,[4] and in lowering abnormally elevated serum calcium.[5, 6] It has been tried with indifferent success as a ureteral irrigant for the dissolution of kidney stones.[7, 8, 9] In this case it is so irritating that patients refuse therapy. An interesting use of solutions of EDTA is for the removal of barium enema impactions.

The first medicinal use of EDTA in this country was for the lowering of excessively elevated serum calcium levels,[6] and as an outgrowth of these studies it was proposed as an anticoagulant.[10, 11, 12] Its use for this purpose is now widespread, particularly for the isolation of platelets. It prevents the clotting of blood by chelating the calcium, thus removing any free calcium ions. EDTA, however, has caused serious renal toxicity, resulting in tubular necrosis, on prolonged administration.[13, 14] For this reason it would be unwise to use EDTA for blood for transfusion. It might also be noted that there are reports that show an effect of EDTA in prolonging prothrombin time.[15, 16] Investigators have shown that this effect is not due

[2] Bailar, J. C.: Chemistry of the coördination compounds, 1956, Reinhold Publishing Company, New York.

[3] Grant, W. M.: New treatment for calcific corneal opacities, A. M. A. Arch. Ophth. **48**: 681, 1952.

[4] Halbertsma, T., and Van Den Brink, C.: Calcinosis universalis, Maand. v. Kind. **24**: 150, 1956.

[5] Popovici, A., Geschicker, C., Reinovsky, A., and Rubin, M.: Experimental control of serum calcium levels in vivo, Proc. Soc. Exper. Biol. and Med. **74**: 415, 1950.

[6] Spencer, H., Vankinscott, V., Lewin, I., and Laszlo, D.: Removal of calcium in man by ethylenediamine tetraacetic acid, J. Clin. Investigation **31**: 1023, 1957.

[7] Raymond, S., and Gehres, R. F.: Ethylenedinitrilotetraacetic acid as a solvent for urinary calculi, Proc. Soc. Exper. Biol. and Med. **74**: 715, 1950.

[8] Marcos de la Mano, J. L.: Estudios sobre la disolucion de los calculos urinarios, Rev. clin. espan. **48**: 247, 1953.

[9] Abeshouse, B. S., and Weinberg, T.: Experimental study of solvent action of versene on urinary calculi, J. Urol. **65**: 316, 1951.

[10] Proescher, F.: Anticoagulant properties of ethylene bis-iminodiacetic acid, Proc. Soc. Exper. Biol. and Med. **76**: 619, 1951.

[11] Hadley, G. G., and Larson, N. L.: Use of sequestrene as an anticoagulant, Am. J. Clin. Path. **23**: 613, 1953.

[12] Wittgenstein, A. M.: Disodium ethylene diamine tetraacetate. An anticoagulant for routine hematological work, Am. J. Med. Technol. **19**: 59, 1953.

[13] Dudley, H. R., Ritchie, A. C., Schilling, A., and Baker, W. H.: Pathologic changes associated with the use of sodium ethylene diamine tetraacetate in the treatment of hypercalcemia, N. England J. Med. **252**: 331, 1955.

[14] Foreman, H., Finnegan, C., and Lushbaugh, C.: Nephrotoxic hazard from uncontrolled edathamil calcium disodium therapy, J. A. M. A. **160**: 1042, 1956.

[15] Zucker M. B.: Some effects of ethylene-diaminetetraacetate (EDTA) on blood coagulation, Am. J. Clin. Path. **24**: 39, 1954.

[16] Wishinsky, H., Weinberg, T., Prevost, E. M., Burgin, B., and Miller, M. J.: Ethylenediaminetetraacetic acid in the mobilization and removal of iron in a case of hemochromatosis, J. Lab. and Clin. Med. **42**: 550, 1953.

to the removal of calcium or magnesium, even though both of these ions are known to be involved in the clotting mechanism. There are indications that nickel is the metal which stabilizes the labile factor, and that the effect of EDTA on the prothrombin time arises from its chelation of nickel.[17]

The second use of EDTA is as a deleading agent for the treatment of lead poisoning.[18, 19] For this purpose it is necessary to administer EDTA as the calcium complex, to prevent the material from lowering blood calcium. Advantage is taken of the fact that lead has about 10,000,000 times the affinity of calcium for EDTA, so that lead present in tissues and fluids quickly combines with EDTA, displacing calcium. This is now the standard method of therapy for lead poisoning.[20-23]

EDTA is not absorbed when administered by the oral route,[24] but its lead chelate is readily absorbed. If lead salts are present in the gastrointestinal tract, EDTA will form a lead chelate which is rapidly absorbed into the blood from which it is soon eliminated through the urinary tract.[25] EDTA must be administered intravenously to chelate lead salts which have already been absorbed since EDTA is not absorbed from the gastrointestinal tract. The lead is so tightly bound to EDTA that it is of low toxicity. This has been considered the explanation of the lack of toxicity of the high blood levels of lead obtained in the course of therapy of lead poisoning with calcium EDTA.[19] The toxicity of the lead chelate is so low that it has been investigated and proposed as a contrast roentgenographic agent.[26] Recent work suggests the value of Ca EDTA aerosol for elimination of heavy metal dust.[27, 28]

EDTA was found useful for bringing about the rapid excretion of many toxic or radioactive metals including copper, gallium, lanthanum, mercury,

[17] Leikin, S., and Bessman, S. P.: The effects of various EDTA complexes on coagulation, J. Hemat. **11**: 916, 1956.

[18] Bessman, S. P., Ried, H., and Rubin, M.: Treatment of lead encephalopathy with calcium disodium versenate, Med. Ann. District of Columbia **21**: 312, 1952.

[19] Bessman, S. P., Rubin, M., and Leikin, S.: The treatment of lead encephalopathy—a method for the removal of lead during the acute stage, Pediatrics **14**: 201, 1954.

[20] Sidbury, J. B.: Lead poisoning. Treatment with disodium calcium ethylene-diamine-tetra-acetate, Am. J. Med. **18**: 932, 1955.

[21] Hardy, H. L., Elkins, H. B., Ruotolo, B. P. W., Quinby, J., and Baker, W. H.: Use of monocalcium disodium ethylene diamine tetraacetate in lead poisoning, J. A. M. A. **154**: 1171, 1954.

[22] Karpinski, F. E., Jr., Rieders, F., and Girsh, L. S.: Calcium disodium versenate in therapy of lead encephalopathy, J. Pediat. **42**: 687, 1953.

[23] Chisholm, J., and Harrison, H. E.: The exposure of children to lead, Pediatrics **18**: 943, 1956.

[24] Foreman, H., and Trujillo, T. T.: The metabolism of C^{14} labeled EDTA in human beings, J. Lab. and Clin. Med. **43**: 566, 1954.

[25] Bradley, J. E., and Powell, A. M.: Oral calcium EDTA in lead intoxication of children, J. Pediat. **45**: 297, 1954.

[26] Shapiro, R.: Chelation in contrast roentgenography with special reference to lead disodium ethylenediaminetetraacetic acid (EDTA), Am. J. Roentgenol. **76**: 161, 1956.

[27] Teisinger, J., and Srbova, J.: Treatment of chronic lead poisoning with calcium versenate, Pracovni Lekarstvi **8**: 163, 1956.

[28] Bisa, K.: Properties of complex-forming substances and their use as aerosols in damage due to suspensions of toxic heavy metals, Z. Aerosol-Forsch. u. Therap. **5**: 209, 1956.

nickel, plutonium, strontium, vanadium, yttrium, zinc,[29] cobalt[30, 31] uranium,[32] and radium-D.[33] It should be emphasized that EDTA and other chelating agents have their greatest effect on heavy metals in body fluids and soft tissues. There is an apparent shift of blood lead from cells to plasma after administration of EDTA.[34] They have only a very limited effect upon metals which have been incorporated into bone structure. Therefore, in case of poisoning with radioactive elements which may be deposited in bone, it is imperative that treatment begin as soon as possible.

EDTA has been used in the treatment of Wilson's disease.[35] Patients with this disease excrete three times as much copper as normal individuals when administered EDTA, confirming the impression that Wilson's disease is a disorder of copper metabolism. Unfortunately EDTA produces no significant improvement in the patients' condition.

EDTA was found to be effective in the treatment of gas gangrene in studies performed on guinea pigs, and mice.[36] It was postulated that this beneficial effect may result from the inhibition of one or more of the toxins through the chelation of some essential metal.

Another group of chelating agents has been under study, all of which have one or more thiol groups. One of these, BAL, has been previously mentioned. It is foul smelling, highly irritating to tissues, and must be given intramuscularly. Even so it is presently the treatment of choice for arsenic, mercury and silver intoxication.

A portion of the penicillin molecule which is an analogue of the amino acid cysteine, known as penicillamine, has turned out to be a useful chelating agent. This compound appears to be active orally and has been used successfully to remove copper in Wilson's disease.[37, 38] It should have the same application as BAL, and since it can be administered by the oral route it should be far more useful.

[29] Chenoweth, M. B.: Chelation as a mechanism of pharmacological action, Pharm. Rev. **8**: 57, 1956.

[30] Munari, M., and Tinazzi, V.: Cobalt poisoning and its treatment with disodium ethylenediaminetetraacetate, Folia med. **39**: 260, 1956.

[31] Ambanelli, U., and Salvi, G.: Influence of ethylenediaminetetraacetic acid and β-mercaptoethylamine on excretion and distribution of cobalt 60, Ateneo parmense **27**: 622, 1956.

[32] Dagirmanjian, R., Maynard, E. A., and Hodge, H. C.: The effects of calcium disodium ethylenediaminetetraacetate in uranium poisoning in rats, J. Pharmacol. and Exper. Therap. **117**: 20, 1956.

[33] Nerurkar, M. K., and Sahasrabudhe, M. B.: Influence of combined administration of vitamin A and calcium ethylenediaminetetraacetate on the elimination of radium D in rats, Proc. Indian Acad. Sc. **44B**: 73, 1956.

[34] Bessman, S. P., and Layne, E. C.: The distribution of lead in blood after Ca EDTA, Am. J. Dis. Child. **89**: 292, 1955.

[35] Cartwright, G. E., Hodges, R. E., Gubler, C. J., Mahoney, J. P., Daum, K., Wintrobe, M. M., and Bean, W. B.: Studies on copper metabolism. XIII. Hepatoventricular degeneration, J. Clin. Investigation **33**: 1487, 1954.

[36] Moskowitz, M.: Metal chelates in gas gangrene, Proc. Soc. Exper. Biol. N. Y. **92**: 706, 1956.

[37] Walshe, J. M.: Wilson's disease; new oral therapy, Lancet **1**: 25, 1956.

[38] Walshe, J. M.: Penicillamine, a new oral therapy for Wilson's disease, Am. J. Med. **21**: 487, 1956.

A third new and powerful chelating agent, beta-mercaptoethylamine, is the substance resulting when carbon dioxide is removed from cysteine. It is also called cysteamine, or thioethanolamine. It has been claimed that this compound reduces radiation injury.[39] Perhaps this is due to its chelating properties but more likely it is the result of its ability to react with free radicals.

There are many naturally occurring chelating agents and they include amino acids, carbohydrates, proteins, and some organic acids such as citric acid. When a chelating agent is administered to an individual, it must compete with these natural chelating agents for metal ions. Toxic metals such as lead and arsenic are bound to tissues through a limited number of groups such as thiol, hydroxy, amino, carboxyl and imidazole. If two or more of these groups are near each other on a protein molecule, the potential for forming a chelate is present.[40] As a consequence, only the most powerful chelating agents such as EDTA are able effectively to capture metal ions.

The natural chelating agents normally present probably serve a physiologic function. At least it can be demonstrated that at normal concentrations they can affect metabolic activity. For example, many of the amino acids enhance markedly the absorption of iron in the gut.[41, 42, 43] Citrate, produced in large amounts by the Krebs cycle, has been used to delead patients with plumbism.[44] Recently, by mild inhibition of citrate oxidation, an accumulation of citrate was produced in lead poisoned animals which effectively stimulated the removal of lead from the tissues.[45]

Probably most of the complex reactions, upon which the vital processes of living organisms depend, are influenced at some stage by natural chelates formed by the union of a metal ion and a protein or some other natural structure. Many bond making and bond breaking reactions of natural processes are catalyzed by metal-enzyme chelates. Heme and chlorophyll are two well known examples of natural chelates. Excellent reviews have been published on this subject.[29]

Porphyrins bind selectively to tumor sites [46] and this has been proposed

[39] Balq, Z. M., Herve, A., Lecomte, J., Fischer, P., and Blavier, J.: Protection contrena rayonnement X par la beta-mercapto ethylamine, Arch. internat. de physiol. **59**: 442, 1951.

[40] Grassmann, W., and Kusch, D.: Über die Bindung von Ag- und Pb-Ionen durch Kollagen, Ztschr. physiol. Chem. **290**: 216, 1952.

[41] Rummel, W., and Candon, B.: How is iron absorbed? A new concept and a new chelate, Internat. Record Med. and Gen. Pract. Clins. **169**: 783, 1956.

[42] Rummel, W., Jacobi, H., and Pfleger, K.: Enteral absorption of minute amounts of iron, Naunyn-Schmiedebergs Arch. exper. Path. u. Pharmak. **228**: 204, 1956.

[43] Pomeranze, J., and Gadek, R. J.: Clinical appraisal of drugs with special reference to a new chelate hematonil, N. England J. Med. **257**: 73, 1957.

[44] Kety, S. S., and Letonoff, T. V.: Lead poisoning, Am. J. M. Sc. **205**: 406, 1943.

[45] Fried, J. F., Rosenthal, M. W., and Schubert, J.: Induced accumulation of citrate in therapy of experimental lead poisoning, Proc. Soc. Exper. Biol. and Med. **92**: 331, 1956.

[46] (a) Figge, F. H. J., Weiland, G. S., and Manganiello, L. O. J.: Cancer detection and therapy. Affinity of neoplastic, embryonic, and traumatized tissues for porphyrins, metalloporphyrins, Proc. Soc. Exper. Biol. and Med. **68**: 640, 1948. (b) Manganiello, L. O. J., and Figge, F. H. J.: II. Methods of preparation and biological effects of metalloporphyrins, reprinted from Bull. Sch. Med. U. Md. **36**: 1951.

as a method of therapy of malignancy. An analogue of heme has been synthesized in which uranium is complexed.[47] The hope of the investigators is that the radioactive metal will be brought selectively to the site of the tumor and held there by the porphyrin with which it is chelated.

Many of our antimicrobial drugs are chelating agents. The antibacterial action of oxine (8-hydroxyquinoline) is dependent upon its ability to form chelates. It penetrates cell membranes as a fat soluble 2:1 complex (2 molecules of oxine in combination with 1 atom of metal), and then exerts its toxic effect inside the cell as the ionic 1:1 complex.[48]

Many of the antituberculous drugs are chelating agents and are known to form chelates in biological systems. These drugs include isoniazid, streptomycin, p-aminosalicylic acid (PAS), thiosemicarbazone, aspergillic acid and usnic acid.[49] The ability of these drugs to form chelates appears to be important for their action but the exact rôle of chelation in their action is yet to be established.

The tetracycline antibiotics form stable chelates with many metals but it is not yet known if their antibacterial action is dependent upon their metal binding properties.[50] However, it is known that factors other than their ability to form chelates are important, since degradation products of the tetracyclines which retain the ability to form chelates are not antimicrobial.[49]

The absorption of orally administered tetracyclines is prevented by alumina,[51] and is inhibited by magnesium sulfate [52] and possibly other metal salts through the formation of chelates which are poorly absorbed. For this reason it is unwise to administer aluminum or magnesium antacids along with the tetracyclines.

Thus it can be said that chelation changes the solubility and ionic activity of metals. Awareness of its rôle in metabolism can lead to a better understanding of all of the reactions which involve metals. By the manipulations of organic synthesis it is possible to devise therapeutic agents of remarkable potency.

SAMUEL P. BESSMAN, M.D.
NORMAN J. DOORENBOS, Ph.D.

[47] Bases, R. E.: Uranyl protoporphyrin: A new uranium complex, Science **126**: 164, 1957.

[48] Rubbo, S. D., Albert, A., and Gibson, M. I.: The bacterial action of 8-hydroxyquinoline (oxine), British J. Exper. Path. **34**: 119, 1953.

[49] Weinberg, E. D.: The mutual effects of antimicrobial compounds and metallic cations, Bact. Rev. **21**: 46, 1957.

[50] Albert, A.: Avidity of Terramycin and Aureomycin for metallic cations, Nature **172**: 201, 1953.

[51] Albert A., and Rees, C. W.: Avidity of the tetracyclines for the cations of metals, Nature **177**: 433, 1956.

[52] Hamburger, M., Carleton, J., and Harcourt, M.: Reversal of the antistaphylococcal action of tetracycline by magnesium, Antibiotics and Chemotherapy **7**: 274, 1957.

REVIEWS

The Nature of Brucellosis. By WESLEY W. SPINK, M.D., D.Sc. 464 pages; 16 × 24 cm. University of Minnesota Press, Minneapolis. 1956. Price, $8.00.

Brucellosis, with all its fascinating complexities, has captured the interest and imagination of students of infectious disease over recent years. The pertinent literature which has accumulated on this subject is now enormous. In this book, Dr. Spink, an outstanding, longtime student of brucellosis, admirably conducts the reader through a comprehensive consideration of the available information in an interesting fashion and has supplemented it with his own extensive experience.

The story of the crystallization of concepts of disease entities may often be as instructive as it is entertaining. Dr. Spink, opening his book with a historical review of the evolution of the concept that brucellosis is a disease of both animals and man, has very thoughtfully included photographs of some of the men and women who have made outstanding contributions over the years. This chapter is followed by a comprehensive consideration of the Brucella organisms and a series of chapters on epidemiological aspects. One of the most outstanding and important chapters is the one on pathogenesis. The pertinent information which has accumulated from attempts to unravel the mysteries of the mechanisms of the disease process is collected together here. The author calls attention to questions which still require elucidation and presents hypotheses yet to be proved. He considers such aspects as the rôle of the intracellular location, the place of phagocytosis, the part played by hypersensitivity and the possibility of cellular immunity. One hardly needs to point out that many of the problems posed in the solution of the pathogenesis of brucellosis find their counterparts in other "intracellular" infections. Hence, this chapter would seem particularly worth the while of students of infectious disease generally. Admirable and comprehensive consideration is also given the natural course of brucellosis in man, its complications, diagnosis, therapy and prevention. Five elaborate appendices are included. One of these records in some detail the protocols of 244 human cases of brucellosis. Finally, but not the least important, is a bibliography of 906 pertinent references.

This book can be recommended without hesitation to the practising physician, clinical investigator and laboratory scientist as an excellent review of brucellosis by an eminent authority in the field.

CHARLES L. WISSEMAN, JR., M.D.

The Practice of Medicine. Edited by JOHN S. RICHARDSON, M.V.O., M.A., M.D. (Cantab.), F.R.C.P. 1076 pages; 16 × 24 cm. Distributed in the U. S. by Little, Brown & Company. 1956. Price, $8.50.

This text, designed primarily for the undergraduate student or pre-general practitioner and compiled by a group of London physicians of consultant and lecturer status in the specialties, presents the substance of what the authors usually teach their students. The whole has been edited by John S. Richardson, Physician, St. Thomas's Hospital, London, who contributed the sections on The Endocrine Glands, The Rheumatic Diseases, Poisons and, with Dudley Baker, the section on The Management of Terminal Disease. Sections are divided generally after the division of the specialties.

The introductory chapter on the nature of disease is particularly arresting in the intertwined history of medicine and the concepts of pathological processes viewed in all their ramifications and arriving at the present-day concept of man and his environment.

The approach to the various system diseases is direct and entails, along with incidence, the usual diagnostic features and treatment. Because of the character of the work, some of the more common entities, as well as the collagen diseases, are treated briefly. Very little is left unmentioned. Sections on Fluid and Electrolyte Disturbances and their correction, Nutrition, and Management of Terminal Disease are very valuable additions to a medical text. The section on psychiatry is well organized and presents the subject in a fashion that is easily understood. Very few minor errors are encountered.

Students and practitioners will find this a complete and well organized text of great value.

A. D. R.

Blood and Bone Marrow Patterns. By G. D. TALBOTT, M.D., formerly Chief of Medicine, 2750th Hospital, and Respiration Section, Aero Medical Laboratories, Wright-Patterson Air Force Base, Dayton, Ohio; ELMER R. HUNSICKER, B.S., formerly Chief of Laboratories, 2750th Hospital, and Respiration Section, Aero Medical Laboratories, Wright-Patterson Air Force Base, Dayton, Ohio; and JONAH LI, M.D., University of California Medical Center, San Francisco. 59 pages; 31 × 24 cm. (loose-leaf). 1957. Grune and Stratton, New York. Price, $12.00.

It is the authors' intent to present in this color atlas the bone marrow patterns of the most commonly encountered hematologic disorders. The first five color plates (30 photomicrographs) picture typical normal bone marrow cells. The following 23 plates (115 photomicrographs) illustrate what the authors consider to represent the characteristic findings on smear preparations in 24 different selected hematologic diseases. There is no text; rather, a series of legends on the facing pages, briefly listing cell descriptions and features comprising cellular patterns.

The color photomicrographs are in general of rather good quality, though there is considerable variation in color reproduction from plate to plate. The appreciation of finer points of cellular morphology still must be gained from microscopic study of the original preparations. Likewise, it is quite difficult to select several very small areas on a slide which when reproduced illustrate adequately the bone marrow pattern typical of a disease. There is no attempt to describe or to illustrate the *normal* marrow pattern. The beginner will find, therefore, some of the abnormal pattern descriptions relatively meaningless. The reviewer is of the opinion that tissue sections of marrow particles are a most valuable aid in appreciating bone marrow pathology. Only one disorder is illustrated in this manner.

The atlas should prove of some value to laboratory technologists and medical students who are beginning marrow studies, and to those who rarely look at such material, mainly through help in recognition of cells. Since it is not widely used, they are likely to find the "rubriblast-rubricyte" nomenclature of erythroid cells a bit cumbersome. Those more experienced will find the book of little value.

C. L. S.

Diabetes Mellitus, with Emphasis on Children and Young Adults. By T. S. DANOWSKI, B.A., M.D. 510 pages; 15.5 × 23.5 cm. The Williams and Wilkins Company, Baltimore, Maryland. 1957. Price, $13.50.

One-fourth of this monograph critically evaluates, and integrates with older concepts, the knowledge of biochemical and hormonal interrelations, pertaining to diabetes mellitus, which has accumulated in the past two decades. Three-eighths discusses the manifestations, the diagnosis, and the treatment of patients with

diabetes mellitus. The remainder deals with diabetic acidosis, the growth and development of diabetic children, and the complications of this disorder. Contrasts between the disease in adults and in children are stressed.

Because of the absence of hokum the volume is comprehensive, exceptionally clear, and relatively small. Some of the author's remarks deserve quotation here. They illustrate his scientific candor; they should refresh the atmosphere of this field of medical practice; they should increase the sale of his book.

"One can speak freely only of one's own cutoms and views on the therapy of diabetes but it is certain that all workers in this field, whether or not they have so stated, have as their goal a long, safe, and useful life for their charges. The fact that there are differences of opinion on how this is to be attained of itself indicates that no one approach has proved itself clearly superior to all others. It is well to recognize that on the whole each of the regimens in use at present can be made to meet the needs of the majority of a clinic's patients. This should be viewed as an index of the adaptability of biologic organisms or of inherent margins of safety and not offered as scientific data which establish the merits of a particular system." (p. 231)

"At various times considerable controversy has been engendered in matching mortality statistics from various institutions as an index of the efficacy of one or the other aspect of coma therapy. The furor and passion seems to have waned with the general recognition that the sum of the characteristics of the population as admitted to a particular institution is often more important than the minor variations in the therapeutic regimen to which they are subsequently subjected." (p. 328)

"Perhaps the most pernicious effect of the view that strict regimentation prevents the vascular complications of juvenile or other long-term diabetes is the distraction of the interest of clinicians and investigators from studies of alternative views." (p. 427)

Other good features include (1) a table of contents which gives an adequate outline of each chapter, (2) helpful introductions to each chapter and pertinent summaries, (3) uncluttered diagrams, (4) presentation of biochemical data by scattergraphs, (5) the use of elementary statistical concepts to determine degrees and significance of abnormality of these data, instead of the use of personal belief and tradition, (6) convenient organization of the bibliography at the end of each chapter, (7) good typography and format on relatively glare-free paper.

Only a few discrepancies appear to have evaded proof reading. NPH insulin is supplied as a cloudy suspension rather than as a clear solution. Tes-Tape for urinalysis, though more convenient than Clinitest, produces a color spectrum too difficult for many patients and nurses to interpret with any accuracy.

This monograph should be digested by internists and pediatricians engaged in teaching medical students, by interns and residents aiding in the care of patients with diabetes mellitus, and by junior physicians working in diabetic clinics. Many "seasoned diabeticians" may become disturbed by it; perhaps their equanimity is not of any greater importance than their enlightenment.

This reviewer feels that this monograph will make historic landmarks of all other currently available textbooks in its field.

PERRY FUTTERMAN, M.D.

Clinical Laboratory Diagnosis. 5th Ed. By SAMUEL A. LEVINSON, M.S., M.D., Ph.D., and ROBERT P. MACFATE, Ch.E., M.S., Ph.D. 1246 pages; 16 × 24 cm. Lea & Febiger, Philadelphia. 1956. Price, $12.50.

Clinical Laboratory Diagnosis, now in its fifth edition, is known to many workers in the field of laboratory medicine as an excellent reference volume. It

has been completely revised by the two authors with the help of five collaborators representing several special fields. A brief review of anatomy, physiology and biochemistry is given, followed by sections on the gastrointestinal tract, on metabolism, blood chemistry, kidney and urine, hematology, bacteriology and immunology, pediatric procedures, blood chemistry and tropical medicine. A brief outline of milk analysis and toxicology is also included. The methods presented are for the most part those used at the University of Illinois Research and Educational Hospitals and the Chicago Board of Health. This approach has the advantage that the methods presented are known to give reliable results in the hands of individuals with various types of training. It has the disadvantage, particularly in the section on blood chemistry, that some of the newer methods are omitted while older methods not in general use are still included.

The authors are to be commended on the general excellence of their book.

M. A.

The Physiology of Induced Hypothermia. Edited by ROBERT D. DRIPPS, M.D. 447 pages; 25.5 × 18 cm. National Academy of Sciences—National Research Council, Washington, D. C. 1956. Price, $3.50.

The Physiology of Induced Hypothermia is a record of a Symposium held in October of 1955 in Washington, D. C. under the auspices of the Division of Medical Sciences of the National Academy of Sciences and the National Research Council.

The Chairman of the Symposium, Dr. Robert D. Dripps, has done a superb job of editing and correlating the wide and varied collection of material. The volume deals first with the physiologic effects of hypothermia on the organism as a whole and then considers the effects on specific systems. It concludes with a discussion of the clinical applications of hypothermia and some of the technics for lowering whole body or specific organ temperature.

The sections dealing with myocardial irritability and the one on animal hibernation are outstanding. Each section is followed by a review and appraisal by one or two of the panelists. These serve to consolidate the facts, to point out discrepancies in data or errors in experimental design and to elucidate areas in which further investigation is indicated.

The comments made during the discussion sessions are included with each paper so that the flavor of the symposium is conveyed to the reader. The bibliography is exhaustive.

This is an excellent volume which presents the experience and opinions of the outstanding workers in the field of induced hypothermia. It brings together in one place a summary of the vast amount of work that has been done in the physiology of induced hypothermia in a relatively short period of time. It also serves to focus attention upon the even greater amount of work that must yet be done before the multiplicity of effects of lowering body temperature in man is fully understood.

This book may be highly recommended as an excellent background source for all those interested in the application of hypothermic technics.

M. H.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Annual Epidemiological and Vital Statistics, 1954. 617 pages; 28 × 21.5 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, $10.00.

Atlas of Clinical Endocrinology, Including Text of Diagnosis and Treatment. By H. Lisser, A.B., M.D., Clinical Professor Emeritus of Medicine and Endocrinology, University of California School of Medicine, San Francisco, etc.; and Roberto F. Escamilla, A.B., M.D., Clinical Professor of Medicine, University of California School of Medicine, San Francisco, etc. 476 pages; 28.5 × 22 cm. 1957. The C. V. Mosby Company, St. Louis. Price, $18.75.

Biology of the Treponematoses, Based on Studies Carried Out at the International Treponematosis Laboratory Center of the Johns Hopkins University under the Auspices of the World Health Organization. World Health Organization Monograph Series No. 35. By Thomas Bourne Turner, Professor of Microbiology, Johns Hopkins University, Baltimore, Md., U. S. A.; and David H. Hollander, Assistant Professor of Microbiology, Johns Hopkins University, Baltimore, Md., U. S. A. 278 pages; 24 × 16 cm. 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, $6.00.

The Clinical Aspects of Arteriosclerosis. By Seymour H. Rinzler, M.D., F.A.C.P., Associate Physician, Beth Israel Hospital, etc. 339 pages; 26 × 18 cm. 1957. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $8.75.

Colorimetric Analysis. Volume I. Determinations of Clinical and Biochemical Significance. 2nd Ed. By Noel L. Allport, F.R.I.C., Consulting Analyst, Official Analyst under the National Health Service Act, etc.; and J. W. Keyser, M.Sc., Ph.D. (Lond.), A.R.I.C., Senior Lecturer in Chemical Pathology, The Welsh National School of Medicine. 424 pages; 23 × 14.5 cm. 1957. The Macmillan Company, New York. Price, $9.00.

Emergencies in General Practice: Specially Commissioned Articles from the British Medical Journal, *January 1955 to June 1956 (Fully Revised).* 470 pages; 22 × 14.5 cm. 1957. British Medical Association, London. Price, 25 s. net.

Erworbene hämolytische Anämien: Klinik und Serologie. By Professor Dr. Med. H. H. Hennemann. 198 pages; 24.5 × 17.5 cm. 1957. VEB Georg Thieme, Leipzig. Price, Gebunden DM 26.40.

From Sterility to Fertility: A Guide to the Causes and Cure of Childlessness. By Elliot E. Philipp, M.A., M.B., B.Chir., F.R.C.S., M.R.C.O.G. 120 pages; 19 × 12.5 cm. 1957. Philosophical Library, New York. Price, $4.75.

Fundamentals of Human Physiology for Students in the Medical Sciences. By W. B. Youmans, Ph.D., M.D., Professor of Physiology, University of Wisconsin. 567 pages; 22.5 × 14 cm. 1957. The Year Book Publishers, Inc., Chicago. Price, $8.50.

General Principles Governing the Use of Food Additives: First Report of the Joint FAO/WHO Expert Committee on Food Additives. World Health Organization Technical Report Series No. 129. 22 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

An Introduction to Blood Group Serology: Theory, Techniques, Practical Applications, Apparatus. By KATHLEEN E. BOORMAN, Senior Scientific Officer, South London Blood Transfusion Centre, Sutton, Surrey; and BARBARA E. DODD, M.Sc. (Lond.), Ph.D. (Lond.), Lecturer in Forensic Medicine, Department of Forensic Medicine, The London Hospital Medical College. 317 pages; 23 × 14.5 cm. 1957. Little, Brown and Company, Boston. Price, $7.50.

It Pays to Be Healthy. By ROBERT COLLIER PAGE, M.D., F.A.C.P. 285 pages; 23.5 × 16 cm. 1957. Prentice-Hall, Inc., Englewood Cliffs, New Jersey. Price, $4.95.

Kaposi's Sarcoma: Multiple Idiopathic Hemorrhagic Sarcoma. Publication Number 308, American Lecture Series. By SAMUEL M. BLUEFARB, B.S., M.D., F.A.C.P., Associate Professor of Dermatology, Northwestern University Medical School, etc. A Monograph in The Bannerstone Division of American Lectures in Dermatology, edited by ARTHUR C. CURTIS, M.D., Chairman, Department of Dermatology and Syphilology, University of Michigan Medical School, Ann Arbor, Michigan. 171 pages; 22.5 × 14.5 cm. 1957. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $5.50.

Methodology of the Study of Ageing. Volume 3 of the *Ciba Foundation Colloquia on Ageing.* Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch.; and CECILIA M. O'CONNOR, B.Sc. 202 pages; 21 × 14 cm. 1957. Little, Brown and Company, Boston. Price, $6.50.

Modern Perinatal Care. By LESLIE V. DILL, M.D., F.A.C.S., Associate Clinical Professor, Obstetrics and Gynecology, Georgetown University School of Medicine, etc. 309 pages;. 24.5 × 16.5 cm. 1957. Appleton-Century-Crofts, Inc., New York. Price, $6.50.

The Ordeal of Gilbert Pinfold: A Conversation Piece. By EVELYN WAUGH. 232 pages; 20 × 13.5 cm. 1957. Little, Brown and Company, Boston. Price, $3.75.

Ph.D. The Philosophy of a Doctor: Experience and Aspiration. By JANVIER W. LINDSAY. 79 pages; 21 × 14 cm. 1957. Pageant Press, Inc., New York. Price, $2.50.

The Premature Baby. 4th Ed. By V. MARY CROSSE, O.B.E., M.D. (Lond.), D.P.H., M.M.S.A., D.(Obstet.) R.C.O.G., Consultant Paediatrician, Little Bromwich General Hospital, etc. 242 pages; 21 × 14 cm. 1957. Little, Brown and Company, Boston. Price, $5.00.

Rheumatoid Arthritis: A Definition of the Disease and a Clinical Description Based on a Numerical Study of 293 Patients and Controls. By CHARLES L. SHORT, M.D., WALTER BAUER, M.D., and WILLIAM E. REYNOLDS, M.D. 480 pages; 24 × 16 cm. 1957. Published for The Commonwealth Fund by Harvard University Press, Cambridge. Price, $7.00.

The Teaching of Hygiene and Public Health in Europe: A Review of Trends in Undergraduate and Post-Graduate Education in Nineteen Countries. World Health Organization Monograph Series No. 34. By F. GRUNDY, M.D., M.R.C.P., D.P.H., Professor of Preventive Medicine, Welsh National School of Medicine, Cardiff; and J. M. MACKINTOSH, M.D., LL.D., F.R.C.P., D.P.H., Professor of Public Health, University of London; with an introduction by JACQUES PARISOT, Formerly Dean of the Faculty of Medicine, University of Nancy. 24 × 16 cm.

1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, $5.00.

The Year Book of Cancer (*1956–1957 Year Book Series*). Compiled and edited by RANDOLPH LEE CLARK, JR., B.S., M.D., M.Sc. (Surgery), D.Sc. (Hon.), Director and Surgeon-in-Chief, The University of Texas M.D. Anderson Hospital and Tumor Institute, Houston, Texas, etc.; and RUSSELL W. CUMLEY, B.A., M.A., Ph.D., Director of Publications, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas, etc. 572 pages; 20 × 13.5 cm. 1957. The Year Book Publishers, Chicago. Price, $7.50.